Psychopharmacology Bulletin

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Psychopharmacology Bulletin
National Institute of Mental Health
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Meeting Announcements

The **Society of Behavioral Medicine**, formerly located at 600 North Wolfe Street, Baltimore, Maryland, is pleased to announce that its national office has moved to Knoxville, Tennessee. The Society's new address is:

The Society of Behavioral Medicine
P.O. Box 8530, University Station
Knoxville, TN 37916
Phone No. 615 974-5164

In addition, the Society's Third Annual Meeting will be held in Chicago, Illinois on March 3-5, 1982 at the downtown Chicago Marriott. This year's meeting will include courses in the fundamentals of behavioral medicine, numerous workshops, practica, symposia, and short courses, and a debate on the "Dangers and Benefits of Exercise." There will also be an invited address by Chandra Patel, M.D., of London, England entitled "A New Dimension on Coronary Heart Disease Prevention."

Inquiries about the Society and the upcoming meeting should be directed to Judith C. Woodward, Administrative Director, at the above address.

• • • •

The **International Conference on Alcoholism** will hold its meeting on March 30-April 4, 1982, in Oxford, England. For information write to: Philip Goldring, Broadway Lodge, Oldmixon Road, Weston-super-Mare, BS24 9NN, Avon, England.

• • • •

The **American Psychological Association** meeting will be held August 23-27, 1982 in Washington, D.C. For information write to: Adelbert H. Jenkins, c/o Candy Won, American Psychological Association, 1200 17th Street, N.W., Washington, D.C. 20036.

• • • •

The **International Congress on Alcoholism and Drug Dependence** will meet on October 9-15, 1982, in Tangier, Morocco. For information write to: International Council on Alcohol and Addictions, P.O. Box 140, CH-1001 Lausanne, Switzerland.

• • • •

An **International Evoked Potentials Symposium** will be held on October 18-20, 1982, in Cleveland, Ohio. For information write to: International Symposium Office, Cleveland Clinic Educational Foundation, 9500 Euclid Avenue, Cleveland, OH 44106.

• • • •

An **International Conference for the Mental Health of the Elderly** will be held in Cairo, Egypt on November 22-25, 1982. Anyone interested in submitting an abstract should forward same to one of the following members of the Program Committee:

Dr. A. Ashour
Secretary General
P.O. Box 290
Heliopolis, Cairo,
Egypt

Dr. Gosta Bucht
Department of Medicine
S. 90185
Umea, Sweden

Dr. Sanford Finkel
230 North Michigan Avenue
Suite 2400
Chicago, IL 60601,
USA

Dr. D. MacLachlan
Toronto General Hospital
101 College Street
Toronto, Ontario M5G 1L7, Canada

• • • •

Books Received

The following new books have recently been received by us for review:

- **GABA and Benzodiazepine Receptors**, Vol. 26 in the series **Advances in Biochemical Psychopharmacology**, edited by E. Costa, G. Di Chiara, and G.L. Gessa. Available from Raven Press, 1140 Avenue of the Americas, New York, NY 10016; Price: U.S. $36.00; 321 pp.

- **Anxiety: New Research and Changing Concepts**, edited by D.F. Klein and J.G. Rabkin. Available from Raven Press, 1140 Avenue of the Americas, New York, NY 10016; Price: U.S. $49.50; 453 pp.

- **Phenomenology and Treatment of Psychophysiological Disorders**, edited by W.E. Fann, I. Karacan, A. Pokorny, and R.L. Williams. Available from SP Medical & Scientific Books, 175-20 Wexford Terrace, Jamaica, NY 11432; Price: U.S. $35.00; 335 pp.

- **Treatment of Migraine: Pharmacological and Biofeedback Considerations**, edited by R.J. Mathew (Proceedings of the Symposium of the Texas Research Institute of Mental Sciences, Houston). Available from SP Medical & Scientific Books, 175-20 Wexford Terrace, Jamaica, NY 11432; Price: U.S. $25.00; 170 pp.

New Journal

Archives of Gerontology and Geriatrics is a new English-language journal published in editorial cooperation with the National Institute of Geriatrics (INRCA), Rome, Italy, and F. Verzar International Laboratory for Experimental Gerontology (VILEG), Ancona, Italy, and Debrecen, Hungary.

The principal aim of the journal is to facilitate the exchange of information between specialists in research in experimental, clinical, and social studies on aging.

Experimental papers dealing with the basic mechanisms of aging at molecular, cellular, tissue, or organ levels will be published. Clinical papers will be accepted if they provide sufficiently new information and are of fundamental importance for the knowledge of human aging. Papers dealing with anti-aging pharmacological presentations in humans are welcome, as are papers on the social aspects of geriatrics. Review papers of interdisciplinary character are especially welcome.

Brief outlines should be sent to the Executive Editor for preliminary consultation:

Dr. Imre Zs-Nagy
Scientific Coordinator of VILEG
University Medical School, VILEG
Hungarian Section
H-4012 Debrecen/Hungary

Book Review

Biochemistry and Pharmacology of Ethanol (Vols. 1 and 2), edited by E. Majchrowicz and E.P. Noble, represent an extensive and scholarly compilation of subjects of interest to researchers and clinicians working in areas related to alcoholism and alcohol abuse. The aim of the editors was to provide in-depth, detailed reviews of the physiological, biochemical, and behavioral effects of alcohol and, in general, this aim has been met. The first volume is devoted mainly to discussion of ethanol metabolism, and to the effects of ethanol on metabolic pathways in peripheral organs and in brain. Detailed attention is given to descriptions of basic research on kinetic mechanisms of alcohol and acetaldehyde metabolism, and more clinically oriented accounts of the interference of ethanol with organ function are also included. In addition, several contributions deal with the often misunderstood or neglected interactions of ethanol with nutritional factors.

The second volume is more concerned with the biochemical, and particularly neurochemical, effects of ethanol. Many of the chapters discuss the possible contribution of ethanol to the important phenomena of intoxication, tolerance, and biochemical and hormonal effects of physical dependence. This volume also contains chapters on ethanol's interactions with other drugs, and discussions of currently popular areas of research, such as the fetal alcohol syndrome, as well as some more neglected but perhaps equally important aspects of alcohol exposure, such as effects on sleep. Within the second volume, several chapters are particularly well prepared. The chapter "Alterations in Neurotransmitter Function After Acute and Chronic Treatment with Ethanol" is a

good example. By analysis of the methodology used in various published reports, the authors greatly clarified an area of research generally plagued with contradictory results. The above-mentioned chapter, "Fetal Alcohol Syndrome: Clinical Pharmacology", is another example of an excellent summary of an important subject area.

Although some unevenness is evident in the quality of the various contributions, in general, they are concise, informative, and substantial in their review of past and current work within each subject area. One especially useful feature for the casual reader, or one who is specifically interested in particular aspects of ethanol biochemistry or pharmacology, is the presence of summaries following each chapter. Because these volumes cover research which is relevant to so many important aspects of alcohol abuse, one wishes that attention could have been given to the psychosocial aspects of alcoholism. Perhaps this topic will be the subject of a later volume.

However, with respect to the biochemistry and pharmacology of ethanol, these two volumes will provide an excellent reference source for readers, both now and in the future.

The books may be ordered directly from the publisher, Plenum Press, 223 Spring Street, New York, NY 10013. Price: U.S.$47.50 (Vol. 1) and U.S.$42.50 (Vol. 2); 704 pp. (Vol. 1) and 574 pp. (Vol. 2).

Boris Tabakoff, Ph.D.
Alcohol & Drug Abuse
Research & Training Program
University of Illinois
Chicago, Illinois

Brief Report

Tardive Dyskinesia: Inter- and Intra-Rating Scale Comparisons

Mary Ann Richardson, M.A.,[1] and Thomas J. Craig, M.D., M.P.H.[2]

Tardive dyskinesia is an iatrogenic movement disorder that affects large numbers of psychiatric patients and as such has become a major public health concern. A multiplicity of assessment methods have been used to both define the prevalence of this disorder and determine the effectiveness of treatment modalities—the most common of these being rating scales (Gardos, Cole, & LaBrie, 1977). Several scales are currently in use which follow two main formats—multi-item scales and scales composed of several global ratings. The Simpson Tardive Dyskinesia Rating Scale (TDRS) and the Simpson Abbreviated Dyskinesia Scale (ADS) (Simpson, Lee, Zoubak, & Gardos, 1979) are examples of the multi-item approach. These scales list and define specific movements to be rated and provide scaling criteria. The Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976) illustrates the combined global rating scale format and lists body areas to be rated and examples of the types of movements to be included within a body area. The lack of uniformity in these and other rating instruments demands that inter- and intrascale data be available to the research community to make possible meaningful comparisons of study results. Unfortunately, little work has been done in this area. Chien, Jung, Ross-Townsend, and Sterns (1977), studying a small group of outpatients, performed interscale correlations on five assessment methods—direct counting, the Gerlach scale, the Crane scale, a portion of the Simpson TDRS scale, and the AIMS scale. The TDRS and the AIMS showed average correlation coefficients to the other four scales of .74 and .73, respectively. The scores of two raters, a medical student and a psychiatrist, were averaged for these analyses. Smith, Kucharski, Oswald, and Waterman (1979) reported that intrascale correlations on the AIMS computed on mean patient scores ranged from .23 to .88. The present study offered the opportunity to perform both inter- and intrascale comparisons of the ADS and the AIMS using ratings collected on a large population of psychiatric inpatients by a single rater.

[1] Clinical Research and Development, Information Sciences Division, Rockland Research Institute, Orangeburg, NY 10962.
[2] Clinical Research and Development, Information Sciences Division, Rockland Research Institute, Orangeburg, New York and Department of Psychiatry, New York University, New York, NY 10024.

Method

One hundred and thirty-two inpatients were evaluated for abnormal movements using the ADS and the AIMS at one rating session per patient by a single rater. Of this group, 40 were females (30.3%) and 92 were males (69.7%). Ages ranged from 19-82 with a mean age of 40 and a median age of 34.5. The Simpson scale was modified by removing tongue tremor, eyelid tremor, the four "other" categories, and by changing the scaling to conform to the five-point scale of the AIMS. The AIMS was modified by removing the "one less" rule for activated movements. Inter- and intrascale correlations were performed using the Pearson product-moment correlation coefficient. For the ADS, intrascale correlations were

obtained for the total scale (Items 1-6, 8-10, 12-14) total facial/oral (Items 1-6), total trunk (Items 8-10), and total extremities (Items 12-14). For the AIMS, intrascale correlations were obtained for the total scale (Items 1-7), global severity (Item 8), total facial/oral (Items 1-4), trunk (Item 7), and total extremities (Items 5 and 6).

Results

Table 1 lists the interscale comparisons. These data demonstrate highly significant correlations between the two scales on total scores, and the total facial/oral and total extremities subscales of .95769, .98096, and .87294, respectively. The total trunk on the ADS and the trunk item on the AIMS show much lower correlations with all other scores.

Table 1

Interscale Correlations* of the ADS and AIMS

	AIMS			
ADS	Total Scale (1-7)	Total Facial/Oral (1-4)	Trunk (7)	Total Extremities (5-6)
Total Scale (1-16)	.95769 $p < .0001$	.84862 $p < .0001$	.43272 $p < .0001$	.61630 $p < .0001$
Total Facial/Oral (1-6)	.84983 $p < .0001$	.98096 $p < .0001$	.19014 $p < .029$	.27279 $p < .0016$
Total Trunk (8-10)	.37841 $p < .0001$	.29113 $p < .0007$	.56167 $p < .0001$	.10438 NS
Total Extremities (12-14)	.67399 $p < .001$	.34387 $p < .0001$	.31225 $p < .0003$	.87294 $p < .0001$

*Pearson "r"

The intrascale correlations are listed in Table 2. The ADS shows a strong correlation for the total scale with the total facial/oral (.86169) and a correlation of .68120 for the total scale with the total extremities. Again, the total trunk score correlates much less strongly with either the total scale, total facial/oral, or total extremities. The total extremities subscale, in addition, showed low correlation with the total facial/oral score.

The AIMS demonstrated a similar pattern with good correlations between the total score and the global severity and total facial/oral items (.85103 and .86971, respectively). In addition, global severity correlated with the total facial/oral score—.72006. The total extremities subscale, however, correlated at a lower level with the total score and global severity items, while the trunk item showed the lowest level of correlation with all other subscales. Despite these variations, all correlations except that between the ADS trunk and extremities subscales achieved statistical significance.

Discussion

This study demonstrates that the ADS and the AIMS correlate well and seem equally efficient in the rating of tardive dyskinesia, despite real differences in format and content. The facial/oral subscales correlate particularly well both in intra- and interscale comparisons. These subscales are perhaps better conceptualized and may possess greater validity for this disorder in this population than the trunk and extremity subscales.

There is a possibility that because these ratings were collected by a single rater at a single session, the reported correlations are somewhat inflated by a carryover effect. On the other hand, interscale correlations performed by multiple raters could be deflated by differences between raters. The lower correlations reported for the trunk and extremity subscales, however, seem to speak against a substantial carryover effect for these data.

In summary, a multi-item rating scale and a scale combining global ratings show strong correlations. The selection of which scale to use will most likely be dictated by the research design. The multi-item scale would be preferable, for example, if the demonstration of differential treatment effects on specific tardive dyskinesia movements is needed; the global approach may be more efficient, for instance, for a large-scale prevalence study where a yes/no designation is all that is required.

The findings also suggest the need for more research into the reason for the relatively low correlations found for trunk and extremity ratings. For example, are these separate manifestations

Table 2

Intrascale Correlations* for ADS and AIMS

ADS \ AIMS	Total	Global Severity	Total Facial/Oral	Trunk	Total Extremities	AIMS
		.85103 $p < .0001$	.88972 $p < .0001$	.46549 $p < .0001$	.85983 $p < .0001$	Total Scale
			.72006 $p < .0001$	.34745 $p < .0001$	.63516 $p < .0001$	Global Severity
Total Facial/Oral	.86169 $p < .0001$			.22188 $p < .01$	.26945 $p < .002$	Total Facial/Oral
Total Trunk	.40905 $p < .0001$		.27139 $p < .0016$		.23713 $p < .006$	Trunk
Total Extremities	.68120 $p < .0001$		.34795 $p < .0001$	.11711 NS		
	Total Scale		Total Facial/Oral	Total Trunk	Total Extremities	
			ADS			

*Pearson "r"

with little physiologic relation to the facial/oral signs representing different patterns of vulnerability (e.g., demographic or clinical) or different underlying mechanisms, or are they merely more difficult to rate? If the former is so, should separate scales be developed rather than lumping all three body areas together into a total score which may obscure significant differences? If the latter, there may need to be a sharpening of diagnostic criteria for these areas.

Acknowledgment: The authors wish to thank Joseph A. Wanderling for programming and statistical assistance, and Frances Simpson for manuscript preparation.

References

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Guy, W. *ECDEU Assessment Manual for Psychopharmacology, Revised, 1976.* U.S. Department of Health, Education, and Welfare, DHEW Publ. No. (ADM) 76-338, 1976.

Simpson, G.M., Lee, J.H., Zouback, B., and Gardos, G. A rating scale for tardive dyskinesia. *Psychopharmacology (Berlin)*, 64:171-179,1979.

Smith, J.M., Kucharski, M.A., Oswald, W.T., and Waterman, L.J. A systematic investigation of tardive dyskinesia in inpatients. *Am J. Psychiatry*, 136:918-922, 1979.

Annual NCDEU Meeting (1981)—Abridged Proceedings

The annual meeting of the New Clinical Drug Evaluation Unit (NCDEU) of the Pharmacologic and Somatic Treatments Research Branch (PST), National Institute of Mental Health, took place on May 26-28, 1981 in Key Biscayne, Florida.

These annual meetings are open meetings sponsored by the PST which focus primarily on recent research findings in psychopharmacology. Updates or reviews of significant issues in this field are also presented.

As in previous years, we are again publishing summaries of the papers presented. We are now listing the titles and authors of all the papers in a panel or plenary session to provide the reader with a better understanding of the content and scope of these sessions. However, in some cases, not all of the papers of a session are included because they were not received before going to press.

NCDEU Update

Chair: Robert F. Prien, Ph.D.
Pharmacologic and Somatic Treatments Research Branch
National Institute of Mental Health
Rockville, Maryland

Neurotransmitter Precursors for the Treatment of Depression

Alan J. Gelenberg, M.D.,[1] Candace J. Gibson, Ph.D.,[2] and Joanne D. Wojcik, R.N., M.S.[3]

The two most widely held biochemical models of depression—the catecholamine (CA) and indoleamine (IA) hypotheses—explain depression as a result of deficient transmission of the CA norepinephrine (NE) or the IA serotonin (5-hydroxytryptamine, 5-HT). Until recently, all drugs used to treat depression appeared to enhance neurotransmission in one or both of these systems, which was used to explain their antidepressant actions. In fact, it was this action of these drugs that gave rise to the models themselves. Another way to increase brain levels of NE and 5-HT, and potentially to increase presynaptic activity, would be the systemic administration of the precursors of the neurotransmitters, an approach something like organic gardening in the brain. For this purpose, the 5-HT precursors tryptophan and 5-hydroxytryptophan (5-HTP), and the NE precursors tyrosine and dihydroxyphenylalanine (DOPA), have been administered to depressed patients. This paper will review some of the theoretical background and clinical experience with these substances, present a view of their current status, and hazard a few predictions regarding the course of future research in this field.

[1] Special Studies Clinic, Erich Lindemann Mental Health Center and Massachusetts General Hospital, Boston, MA 02114.
[2] Laboratory of Neuroendocrine Regulation, Massachusetts Institute of Technology, Boston, MA 02114.
[3] Special Studies Clinic, Erich Lindemann Mental Health Center and Massachusetts General Hospital, Boston, MA 02114.

Monoamine Hypotheses of Affective Disorders

Antidepressant Drugs

The CA and IA hypotheses of affective disorders, largely derived from the pharmacology of drugs that produce or reverse depression in humans and animals, suggest that central monoamine (MA) deficits—particularly of NE or 5-HT—may lead to depression (Maas, 1975; Schildkraut, 1965; Schildkraut & Kety, 1967). Both monoamine oxidase (MAO)-inhibitors and tricyclic antidepressants appear to potentiate the effective level of MAs at the synapse: MAO inhibitors inhibit MA degradation, increasing levels in brain; tricyclics inhibit brain MA uptake mechanisms, prolonging the action of MA at the synaptic receptor. Among the currently available tricyclic antidepressants, the secondary amine compounds (i.e., desipramine, nortriptyline, and protriptyline) are more potent inhibitors of NE-uptake in vitro and in vivo than the tertiary amines (amitriptyline, imipramine, and doxepin), which more selectively block 5-HT-reuptake (Bopp & Biel, 1974). However, all three tertiary amine tricyclics are metabolized in vivo to active secondary amines. Thus, administration of either a tertiary or a secondary amine tricyclic results in a blockade of NE reuptake. A novel approach to the treatment of depression, which is consistent with the CA hypothesis, has been the administration of a **β-adrenergic stimulating drug, salbutamol** (Lecrubier, Puech, Frances, et al., 1981).

Recently, questions have been raised about the role of uptake inhibition in the mechanism of tricyclic antidepressant action. For example, inhibition of reuptake occurs almost immediately, yet reversal of depressive symptoms typically requires several weeks of drug treatment. Despite these questions, the focus of attention remains on MA neurotransmission. Recent data suggest that following several weeks of tricyclic administration, changes may occur in the sensitivity of pre-and postsynaptic MA receptors (Maas, 1979; Sulser, Vetulani, & Mobley, 1978). Thus, via a receptor-mediated feedback mechanism, the neuronal firing rate may be altered and/or postsynaptic receptor sensitivity to the MA "message" may be readjusted. Although the advent of some newer classes of antidepressants has even thrown into question the primacy of NE and 5-HT in the genesis of depression and the action of antidepressant compounds (Gelenberg, 1980), the CA and IA theories still have considerable heuristic value and clinical relevance.

Postmortem Studies: Biochemical findings in depressed patients have provided some support of the MA theories. Postmortem findings in the brains of depressed patients who committed suicide have suggested central deficits in 5-HT. Decreased concentrations of 5-HT and its major metabolite, 5-hydroxyindole acetic acid (5-HIAA), have been found in the brainstem—particularly in the raphe nuclei, which contains cell bodies of 5-HT neurons (Birkmayer & Riederer, 1975; Lloyd, Farley, & Deck, 1974). No deficits in NE or dopamine (DA) have been found (Bourne, Bunney, Colburn, et al., 1968). A recent study, which examined brains from endogenously depressed patients who died of cardiac failure or pneumonia, reported no significant NE deficits but did find extensive decreases in levels of the major NE metabolite, 3-methoxy-4-hydroxyphenylglycol (MHPG), in 6 of 14 areas examined (Riederer, Birkmayer, Seeman, & Wuketich, 1980). This suggests that although NE levels are normal, brain NE turnover may be decreased in some depressed patients.

Cerebrospinal Fluid (CSF): Biochemically, depression may represent a heterogenous disorder, with subgroups of patients who have decreased NE function and normal 5-HT, others with decreased 5-HT and normal NE, and still others with normal values for both systems (Garver & Davis, 1979; Maas, 1975). Furthermore, this heterogeneity in biochemical measurements may underlie a possible heterogeneity in treatment response. For example, Maas has suggested that patients with NE deficits are more responsive to NE-augmenting therapies (e.g., desipramine or amphetamine), while those with 5-HT deficits will respond preferentially to 5-HT-augmenting treatment (e.g., amitriptyline, tryptophan, or 5-HTP) (Maas, 1975). Not all studies, however, support this dual-amine concept or differential drug responsiveness among patients (Ridges, Bishop, & Goldberg, 1980).

Studies of CSF MAs and metabolites have not

been conclusive in confirming an MA theory of affective disorders (van Praag, 1980a, 1980b). In general, CSF levels of NE and its major metabolite, MHPG, are elevated in manics when compared with depressed patients. Reported levels in depressed patients have been less consistent —sometimes lower (Gordon & Oliver, 1971), sometimes the same as those in neurological controls (Post, Lake, Jimerson, et al., 1978; Shopsin, Wilk, Gershon, et al., 1973). These discrepancies could be due to the putative biochemical heterogeneity of depressive disorders: Decreases in CSF NE levels in a subgroup of patients might be obscured when means among a diverse group are compared to controls. Also, many of these studies do not distinguish depressives with a history of mania (bipolars) from those with no previous episodes of mania (unipolars and first-episode depressives).

As with CSF MHPG, baseline levels of lumbar CSF 5-HIAA, the 5-HT metabolite, are decreased in some, but not all depressed patients (Åsberg, Thoren, & Traskman, 1976; Papeschi & McClure, 1971; van Praag, 1980). However, in assessing 5-HT turnover in brain, a complicating factor is that a substantial portion of 5-HIAA measured in lumbar samples is derived from the spinal cord and may not reflect brain 5-HT metabolism. It seems there is a gradient of CSF 5-HIAA concentration: Levels in ventricular fluid are four to five times higher than those in lumbar fluid. When brain ventricular CSF was sampled directly, concentrations of 5-HIAA were lower in patients with endogenous depression, compared to levels in other psychiatric patients and in a neurological control group (Bridges, Bartlett, & Sepping, 1976).

A dynamic measure of central 5-HT turnover can be obtained by administering probenecid, which blocks the transport of acidic metabolites out of CSF, so that their rate of accumulation can be used as an index of 5-HT turnover (Goodwin, Post, Dunner, & Gordon, 1973). Studies using the probenecid technique report that 5-HIAA accumulation was decreased in 40 to 50% of depressed patients (Goodwin et al., 1973; van Praag, 1980). Interestingly, this same subgroup of patients has been reported to improve during treatment with the 5-HT amino acid precursor, 5-HTP (van Praag, 1980) (more about this later).

Urinary Metabolites: Studying urine to figure out what is happening in the brain has been compared to analyzing the Potomac river in an attempt to determine what the President had for lunch. Nevertheless, urinary MA metabolites are more accessible than brain, CSF, or even blood. The most studied of the urinary MA metabolites in depression is the major NE metabolite MHPG. A majority of urinary MHPG is supposedly derived from central nervous system (CNS) NE metabolism, which suggests that MHPG levels should reflect central NE turnover (deMet & Halaris, 1969). However, this remains controversial: Estimates of central contributions of MHPG to the urine pool range from 20 to 70% (Blombery, Kopin, Gordon, et al., 1980; Maas, Hattox, & Greene, 1979).

Like CSF levels of NE and MHPG, urinary levels of MHPG are also elevated in the manic phase of bipolar illness, in contrast with the depressive phase (Jones, Maas, Dekirmenjian, & Fawcett, 1973; van Praag, 1980). In bipolar patients, changes in urinary MA metabolites appear to precede mood swings (Jones et al., 1973), and there is general agreement that depressed bipolars excrete less MHPG than healthy controls (Jones et al., 1973; Jones, Maas, Dekirmenjian, & Sanchez, 1975; Schildkraut, Orsulak, Schatzberg, et al., 1978a; Schildkraut, Orsulak, LaBrie, et al., 1978b). In unipolar depressives, however, equivocal results have been obtained. Some reports indicate lower excretion in unipolar endogenous depressives as compared with healthy controls or patients with characterological depressions (Schildkraut et al., 1978a; Schildkraut et al., 1978b), but others do not (Beckmann & Goodwin, 1980). Earlier reports on this question are hard to interpret because they failed to specify depressive subtypes—e.g., bipolar or unipolar, primary or secondary, endogenous or other.

For proper design and interpretation of studies, it must be noted that the normal range of daily urinary MHPG excretion is very wide—900 to 3,500 mg daily (Hollister, Davis, Overall, & Anderson, 1978). This may be influenced by diet (Muscettola, Wehr, & Goodwin, 1977), mental state and anxiety (Sweeney, Maas, & Heninger, 1978), physical activity (Ebert, Post, & Goodwin, 1972), and state of sympathetic nervous system activity (Cymerman & Francesconi, 1975; Hollister, Prusmack, Knopes, & Kanaske, 1980; Izzo,

Horwitz, & Kaiser, 1979). Furthermore, the observed MHPG decreases in unipolar patients are small: The range of MHPG excretion in unipolar depressed patients is 800 to 3,020 μg daily (Hollister, Davis, & Berger, 1980). Therefore, unless conditions such as diet, activity, and stress are carefully controlled in both subjects and healthy controls, variations within the normal range may obscure differences.

Several groups of investigators have observed a correlation between pretreatment urinary MHPG excretion and drug response. Specifically, depressed patients who excrete the lowest amounts of urinary MHPG tend to show a better response to drugs which act primarily on NE systems, compared to depressed patients with high levels of urinary MHPG (Bechmann & Goodwin, 1975; Fawcett, Maas, & Dekirmenjian, 1972; Hollister et al., 1980). However, there is not universal agreement on this point (Ridges, Bishop, & Goldberg, 1980).

Urinary 5-HIAA is even more susceptible than MHPG to environmental, dietary, and peripheral variations, and is therefore not a reliable index of central nervous system function (Nomra, Colmenares, & Wurtman, 1977).

Precursors

Biochemical Background

In mammalian brain, the CAs, DA and NE, and the IA, 5-HT, are synthesized from their amino acid precursors, L-tyrosine and L-tryptophan, respectively (Wurtman, 1980). The initial and rate-limiting steps in their syntheses are the hydroxylation of the aromatic ring of tyrosine by tyrosine hydroxylase (Nagatsu, Levitt, & Udenfriend, 1964) to form DOPA and the hydroxylation of the indole core of tryptophan by tryptophan hydroxylase (Friedman, Kappelman, & Kaufman, 1972) to form 5-HTP. Both of these amino acid intermediates—DOPA and 5-HTP—are rapidly decarboxylated by the enzyme aromatic L-amino acid decarboxylase to form the amine neurotransmitters DA and 5-HT (Lovenberg, Weissbach, & Udenfriend, 1962). In neurons that contain the enzyme dopamine-β-hydroxylase, DA is converted to NE (Axelrod, 1972).

The enzyme tryptophan hydroxylase is not normally saturated with its amino acid substrate in vivo and, therefore, the rate of brain 5-HT synthesis can be influenced by changes in brain tryptophan concentration (Fernstrom & Wurtman, 1971). Brain tryptophan concentration, in turn, varies directly with its plasma concentration and indirectly with the sum of the plasma concentration of the other large neutral amino acids (LNAA)—leucine, isoleucine, valine, phenylalanine, tyrosine—which compete with it for uptake into the brain (Fernstrom & Wurtman, 1972). Thus, tryptophan administration, or the ingestion of a carbohydrate-containing meal (which elicits insulin secretion, thereby lowering the plasma level of competing LNAAs), results in increases in brain tryptophan and, hence, in brain 5-HT.

It also has been said that the blood concentration of non-albumin-bound tryptophan determines the rate of tryptophan uptake into brain, but this remains controversial (Young & Sourkes, 1977).

Just as tryptophan hydroxylase is not fully saturated in vivo, the same holds true for tyrosine hydroxylase. Only 75% of tyrosine hydroxylase is saturated, as estimated by Carlsson and Lindqvist (1978). This means that raising (e.g., by tyrosine injection or consumption of a protein-containing meal) or lowering (by injection of a competing LNAA) brain tyrosine concentrations in rats can cause parallel changes in CA synthesis, as measured by the rate at which brain DOPA accumulates after decarboxylase inhibition (Gibson & Wurtman, 1977; Wurtman, Larin, Mostafapour, & Fernstrom, 1974). However, increases in brain tyrosine levels lead to increased NE release, as measured by the accumulation of the NE metabolite 3-methoxy-4-hydroxyphenylglycol sulfate (MHPG-SO|) (after probenecid, which blocks its egress from rat brain, or in animals subjected to cold stress, which increases NE turnover in brain) (Gibson & Wurtman, 1978).

In the basal state, DA neurons may be less dependent on tyrosine levels than NE neurons. Thus, administration of tyrosine to animals receiving probenecid does not result in further increases in the major DA metabolite, homovanillic acid (HVA). However, when DA receptors are blocked by pretreatment with haloperidol, thereby accelerating the firing rates of DA neurons,

tyrosine does significantly elevate striatal HVA (Scally, Ulus, & Wurtman, 1977). Similarly, lesions that deplete DA stores and increase firing and turnover in central DA neurons also appear to increase the effects of tyrosine administration.

The response to tyrosine in NE systems also is enhanced when neuronal firing and amine turnover are increased. In hypertensive rats, tyrosine administration results in decreased blood pressure and increased concentration of NE metabolites in the brainstem (Sved, Fernstrom, & Wurtman, 1979). Presumably, NE neurons in the brainstem of these animals are deficient to start, which results in hypertension. The exisiting NE neurons are firing rapidly in a vain attempt to lower the pathologically elevated blood pressure. In this situation, tyrosine can enhance NE release, leading to increased NE transmission in the brainstem and deceased peripheral sympathetic outflow, which serves to lower blood pressure.

Probably the ability of tyrosine to accelerate CA synthesis depends quantitatively on the firing frequency of CA-containing neurons. Therefore, it is possible that in disease states characterized by deficiencies in NE or DA, in which neurons may be firing more rapidly (in an attempt to compensate for the deficiencies), there could be greater sensitivity of CA neurons to tyrosine administration.

The intermediate metabolites DOPA and 5-HTP also have been administered experimentally to increase central CA and IA activity, respectively, since they readily traverse the blood-brain barrier. Normally, concentrations of DOPA and 5-HTP in the brain are undetectable (Carlsson & Lindqvist, 1978); as soon as they are formed, they are rapidly decarboxylated to the neurotransmitters DA and 5-HT, respectively.

Although it is a precursor of the CA's DA and NE, DOPA can be transported into IA, as well as CA neurons. In DA neurons, DOPA is decarboxylated to DA and acts to replace the endogenously occurring neurotransmitter. In 5-HT neurons it is decarboxylated to DA and can displace or release 5-HT from its normal sites (Ng, Chase, Colburn, & Kopin, 1970), thus acting as a false neurotransmitter and interfering with normal 5-HT function. Therefore, DOPA administration leads to increased brain DA but decreased 5-HT; NE remains relatively unaffected (Everett & Borcherding, 1970; Karobath, Diaz, & Huttunen, 1971).

Under normal conditions, then, tyrosine may be preferable for increasing NE synthesis, while DOPA appears more specific for increasing DA synthesis. Furthermore, tyrosine administration has fewer effects on the IA system; although both may decrease brain tryptophan uptake competitively (Rieder, 1980), DOPA can also displace 5-HT from its storage sites, further decreasing brain 5-HT (Karobath et al., 1971).

Just as DOPA enhances CA activity at the expense of IA activity, the IA precursor 5-HTP creates the opposite problem. The administration of 5-HTP effectively raises brain 5-HT, but displaces NE after decarboxylation in CA-containing neurons and lowers brain NE in experimental animals (Lichtensteiger, Mutzner, & Langemann, 1967).

Compared to the intermediate precursors DOPA and 5-HTP, tyrosine and tryptophan may be more specific in increasing their respective neurotransmitters, NE and 5-HT. Their conversion depends on uptake into neurons containing the specific enzymes tyrosine or tryptophan hydroxylase, which are highly localized to those cells containing NE and 5-HT, respectively (Friedman et al., 1972; Nagatsu et al., 1964). Although they can compete with one another for uptake into brain, this effect is less than that seen with L-DOPA or 5-HTP on an equimolar basis.

The possibility has been raised that some depressed patients may have a reduced ability to convert orally administered tryptophan to 5-HTP (van Praag, 1980). It is conceivable that in such individuals, administration of the precursor 5-HTP may be more advantageous than treatment with tryptophan. Similarly, one could speculate that if a similar situation exists regarding NE, some depressed patients might respond preferentially to DOPA.

Precursor Studies in the Treatment of Depression

Unlike the biogenic amines DA, NE, and 5-HT, their precursors—DOPA, tyrosine, 5-HTP, and tryptophan—easily cross the blood-brain barrier. Thus, the precursors can be administered systemically to increase their respective amines' rates of synthesis. L-DOPA raises brain DA level, as measured by increased CSF HVA (Bunney, Brodie, Murphy, & Goodwin, 1971). L-DOPA

probably has little effect on NE level and may actually decrease brain 5-HT, as observed by decreases in CSF 5-HIAA (Goodwin et al., 1973; Bunney et al., 1971). Tryptophan and 5-HTP both raise brain 5-HT levels, producing increases in CSF 5-HIAA (Goodwin et al., 1973; van Praag, 1980). 5-HTP appears to compete with tyrosine's entry into brain, which probably lowers DA activity and has been observed to produce decreased CSF HVA levels (Meyer, Welch, Deshmukh, et al., 1977). Orally administered tyrosine raises plasma tyrosine in man and increases urinary excretion of NE and MHPG (Glaeser, Melamed, Growdon, & Wurtman, 1979).

CA precursors: DOPA—Several trials of DOPA (with and without peripheral decarboxylase inhibitors) for the treatment of endogenous depression have been conducted. Results have generally been poor (Bunney et al., 1971; Carroll, 1972; Dunner & Fieve, 1975; Goodwin et al., 1971; Klerman, Schildkraut, Hasenbush, et al., 1963; Mendels, Stinnett, Burns, & Frazer, 1975; Murphy et al., 1973, Persson & Wålinder, 1971; van Praag, 1977,1980), although DOPA may activate some patients with psychomotor retardation. Among patients with prior manic episodes, periods of hypomania have sometimes been induced (Bunney et al., 1971; Goodwin et al., 1971; Murphy et al., 1973), which were alleviated by decreasing or discontinuing DOPA. Additionally, psychotic features have often been aggravated by DOPA (Goodwin et al., 1971).

It is conceivable that the clinical effects of DOPA are due to increases in brain DA, rather than NE activity. In fact, urinary and CSF levels of the DA metabolite HVA increase linearly with the administered dose of DOPA, but urinary concentrations of the NE metabolite MHPG do not increase until doses of DOPA exceed 4 g (Bunney et al., 1971; Goodwin et al., 1971). Furthermore, as noted earlier, DOPA administration can decrease central 5-HT activity, which might make some patients more depressed. In fact, some parkinsonian patients who receive high doses of DOPA actually develop severe depression (Goodwin et al., 1971). Also, some of the unwanted effects associated with DOPA have been attributed to its competition with uptake and lowering of brain levels of tyrosine and tryptophan (Lichtensteiger et al., 1967). L-DOPA is also associated with many other unwanted and toxic effects such as nausea and vomiting, blood pressure changes, and cardiac rhythm disturbances (Langrall & Joseph, 1972).

CA precursors: Tyrosine—Few trials with tyrosine have been conducted, since it had been believed that the enzyme tyrosine hydroxylase was fully saturated in vivo, and hence that no increase in CA levels could be achieved by tyrosine administration. Indeed, no change in brain NE *levels* is seen in animals treated acutely with tyrosine; however, significant increases do occur in the *rate* of synthesis (Carlsson & Lindqvist, 1978; Gibson & Wurtman, 1977; Wurtman et al., 1974). In addition, re-evaluations of the amount of saturation of tyrosine hydroxylase have suggested that normally it is 75% saturated, so that there is some leeway for increasing synthesis. Moreover, when conditions of deficient CA neurotransmitters exist, the effect of exogenous tyrosine is even more pronounced. As discussed earlier, for instance, tyrosine injection increases the level of MHPG-SO_4 in the brainstem of spontaneously hypertensive rats and lowers blood pressure by a central mechanism (Sved et al., 1979). Therefore, tyrosine may be more specific than other means for increasing brain NE synthesis, particularly if there is a preexisting deficiency. This could make tyrosine particularly useful for treating human diseases characterized by such a deficiency.

One early report on the use of tyrosine in depression failed to find an effect, but there was no indication of the dose used or the length of treatment (Carroll, 1972). In 1980, we published the results of a single-case, placebo-controlled, double-blind crossover trial (Gelenberg, Wojcik, Growdon, et al., 1980). A 30-year-old woman with primary unipolar depression had to discontinue an antidepressant drug because of unwanted effects. As an alternative, she was treated with tyrosine, 100 mg/kg/day by mouth, in three divided doses. Her depression improved markedly after 2 weeks of tyrosine therapy, and within 1 week of placebo substitution her depressive symptoms began to return. The reinstitution of tyrosine therapy was followed by a marked improvement in depression. No adverse effects were noted. Plasma tyrosine levels drawn 2 hours after a dose were approximately double those measured during placebo ingestion. Soon after, Goldberg

reported symptom improvement following nonblind administration of tyrosine to two patients who had previously responded to amphetamine (Goldberg, 1980). Perhaps in these patients tyrosine was specifically correcting an NE deficiency, since amphetamine responders have been found to have relatively low levels of urinary MHPG (Fawcett et al., 1972).

We now have data on an additional six patients who have entered an ongoing double-blind, placebo-controlled pilot study. Three patients were randomly assigned to placebo and three to oral tyrosine (100 mg/kg/d, in three divided doses), for a 4-week trial. During tyrosine treatment, the mean score on the Hamilton Depression Rating Scale (HAM-D) was reduced by 55%, from a initial mean of 21.7 to a final score of 9.7 (*see* Table). In the placebo group, only a small reduction occurred, from an initial mean score of 25.7 to a final mean of 21.3. The three tyrosine-treated patients showed impressive improvement on their HAM-D scores (Table), while two of the three placebo patients had to be withdrawn from the study: One patient deteriorated and became suicidal; the other asked to be removed from treatment because of lack of improvement.

Table

Hamilton Score Changes with Tyrosine and Placebo

Patient	Age	Sex	Hamilton Depression Rating Scale (HAM-D) Initial Score	Final Score*
Tyrosine (100 mg/kg)				
1 (KC)	36	M	22	19
2 (FB)	41	M	20	3
3 (JS)	56	F	23	7
Mean ± SE			21.7 ± 1.5	9.7 ± 8.3
Placebo				
4 (NM)	46	M	25	18
5 (JB)	45	M	30	21
6 (DG)	51	M	22	25
Mean ± SE			25.7 ± 4.0	21.3 ± 3.5

*Final score was determined 4 weeks after beginning of treatment, except for Patients #4 and #6, who were withdrawn from the study early and evaluated at the time of withdrawal, 15 days and 7 days, respectively.

Interestingly, there seems to be a correlation between the change in HAM-D score (pretreatment vs. posttreatment) and the change in fasting plasma tyrosine level (percent change from initial level) (*see* Figure), which is similar to what has been reported during tryptophan therapy (Chouinard, Young, Annable, & Sourkes, 1979).

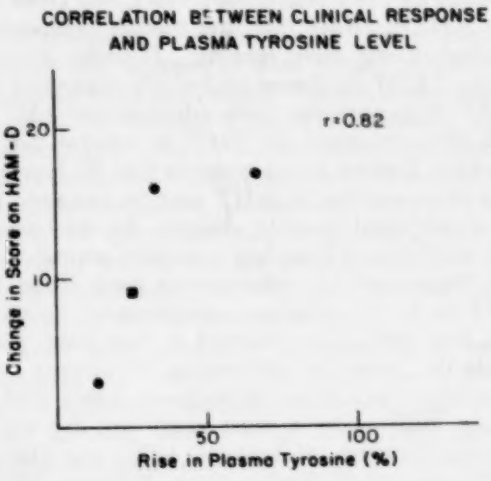

FIGURE. Correlation between clinical response and plasma tyrosine level.
● = patients receiving tyrosine
■ = patients receiving placebo

Change in score on the Hamilton Depression Rating Scale represents the initial value (Day 0) minus the final value (Day 28).

Rise in plasma tyrosine represents the percent increase in fasting plasma tyrosine level on Day 28 from the initial level on Day 0. Tyrosine was measure fluorometrically by the method of Waalkes and Undenfriend.

Other studies have suggested possible abnormalities of peripheral amino acid metabolism in depression. There are indications that peripheral tyrosine metabolism and uptake into brain may be altered in depressed patients. The normal 11 a.m. peak in blood tyrosine level is absent in the depressed phase (Benkert, Renz, Marano, & Matussek, 1971; Kishimoto & Hama, 1976), and there may be less transport of tyrosine into brain (Gaillard & Tissot, 1979). Even if these metabolic

changes are not primary factors in the genesis of depression, decreases in plasma tyrosine could aggravate existing central compromises in NE function.

IA precursors: 5-HTP—The use of the intermediate precursor of 5-HT, 5-HTP, for the treatment of depressed patients was reviewed recently by van Praag (1980). His group chose to use 5-HTP, rather than the mother compound tryptophan, for three reasons: 1) unlike tryptophan, 5-HTP is almost exclusively converted to 5-HT; 2) in animals, orally administered 5-HTP is partly converted to 5-HT in central 5-HT neurons; 3) their group suggests that the conversion of tryptophan to 5-HT may be impaired in some depressed patients, whereas the conversion of 5-HTP to 5-HT appears to remain normal. Dr. van Praag and his collaborators have found 5-HTP to be an effective antidepressant acutely, and they have also reported it may have prophylactic value in preventing recurrences of depression (van Praag & deHaan, 1980; 1981). These findings have been confirmed by some (Angst, Woggon, & Schoepf, 1977; van Hiele, 1980), but not all (Brodie, Sack, & Siever, 1973; Takahashi, Takahashi, & Masamura, 1976) investigators.

Assuming the possibility that 5-HTP is an effective antidepressant, negative results may have reflected some or all of the following:

1) Study Design: Some studies used numbers of patients that were inadequate to establish significant differences from placebo. Moreover, in some, patients were treated for periods of time (1 to 2 weeks) that are too brief to test antidepressant effects.

2) Dosages: There is a probability that 5-HTP has a "therapeutic window" (van Praag, 1980). In some studies, dosages may have been inadequate; in others, excessive levels of 5-HTP could have resulted in decreases in DA and NE concentrations and activity, leading to countertherapeutic outcomes.

3) Selection of Patients: There is evidence that a subgroup of depressed patients might have a "serotonergic" depression and, in fact, patients who exhibit increased accumulation of 5-HIAA in CSF after probenecid administration have been reported to respond best to 5-HTP therapy (van Praag & deHaan, 1979). Also, there is preliminary evidence that 5-HTP may enhance the action of the serotonergic tricyclic antidepressant clomipramine and MAO inhibitor antidepressants (van Praag, 1980).

Dr. van Praag typically administers 5-HTP in combination with an agent such as carbidopa, which inhibits peripheral decarboxylase. This diminishes the conversion of 5-HTP to 5-HT outside of the brain, thereby a) increasing the amount of 5-HT that is centrally available, and b) decreasing unwanted effects. One of the most common and limiting of these unwanted effects has been gastrointestinal upset, attributed to direct effects of 5-HTP on stomach and intestinal walls. To circumvent this problem, Dr. van Praag uses an enteric-coated capsule.

IA precursors: Tryptophan—Tryptophan has undergone many trials as an antidepressant (Bunney et al., 1971; Carroll, 1972; Chouinard et al., 1979; Dunner & Fieve, 1975; Mendels et al., 1975; van Praag, 1977; van Praag, 1980), but unfortunately no consensus has emerged about its efficacy. In fact, a "weigh in" of positive vs negative data would likely be equal. Several excellent reviews over the past few years have evaluated the wide range of studies of tryptophan as an antidepressant (Cole, Hartmann, & Brigham, 1980; Cooper, 1979; Growdon, 1979; van Praag, 1980; Wirz-Justice, 1977).

As was the case with 5-HTP, we will make the assumption that tryptophan actually has some merit as an antidepressant and will attempt to explain the negative data. There is a heuristic advantage to this approach, as it can help in the design of future studies.

1) Inadequacy of study design—Similar to the case with 5-HTP, some studies with tryptophan have used inadequate patient samples for too brief periods of time.

2) Dosage—Evidence has emerged of a possible "therapeutic window" for tryptophan: in six separate studies in which tryptophan was found to be an effective antidepressant, the mean dose was 6 g/day; in seven other studies in which it was ineffective, the mean dose was 8.7 g/day (Young, Gibson, & Gauthier, in press). There is evidence that the therapeutic range may be different for bipolar compared to unipolar patients (Goldberg, 1980). There is also evidence that the co-administration of an inhibitor of tryptophan pyrrolase in

liver may shift the therapeutic window toward lower doses (Goldberg, 1980).

Possible explanations for the therapeutic window include: a) greater induction at higher tryptophan doses of the liver enzyme tryptophan pyrrolase, which catabolizes tryptophan; b) competition of tryptophan with tyrosine for uptake into brain, so that excessive doses would lower brain NE synthesis; c) increased formation at high doses of other active amines, such as tryptamine, which may adversely affect normal 5-HT function (Young et al., in press).

It is interesting that several more recent studies failed to find an antidepressant effect of tryptophan (Cooper & Datta, 1980; Wålinder, Carlsson, Persson, & Wallin, 1980). In each, the dosages were above the therapeutic window determined by Chouinard (1979).

3) Heterogeneity of patients—As noted above, there is evidence that bipolar and unipolar patients may respond differently to tryptophan. In addition, as was the case with 5-HTP, it is conceivable that only those patients whose depression is characterized by low 5-HT activity will respond selectively to tryptophan treatment.

Another source of interpatient variability concerns plasma levels of amino acids. Brain tryptophan concentrations is determined, in part, by the ratio of plasma tryptophan to the plasma concentrations of competing LNAA (see page 10). Consistent with this observation, Møller and colleagues have reported that patients with the lowest tryptophan/LNAA ratio achieved a remission frequency of 80% by Day 14 of tryptophan therapy, while patients at the higher end of the spectrum did not benefit from tryptophan more than from placebo (Møller, Kirk, & Honore, 1980). Therapeutic efficacy has also been related to increases in fasting plasma tryptophan during tryptophan treatment: the larger the increase, the greater the improvement in score on a standard depression rating scale (Chouinard et al., 1979).

4) Interaction with other antidepressants—Until more is known about the effects of administering tryptophan alone, it may be difficult to puzzle out the effectiveness of tryptophan as an adjunct to antidepressant drug therapy. For example, Wålinder and associates (1976) found that tryptophan hastened the onset of therapeutic action of clomipramine, a particularly potent inhibitor of 5-HT uptake (although one whose active metabolite also blocks NE uptake). By contrast, however, Wålinder and his colleagues were unable to find any advantage of combining tryptophan with zimelidine, an even more potent inhibitor of 5-HT uptake Wålinder, Carlsson, & Persson, 1981).

Conclusion

Although none of the amino acid precursors can do for depression what penicillin does for pneumococcal pneumonia, there is every reason to continue clinical trials with tyrosine, tryptophan, and 5-HTP. Unfortunately, the lack of pharmaceutical industry support to fund studies on these substances, coupled with the easy availability of the amino acid tryptophan, has resulted in widespread use of this substance and many publications but, at least until recently, little in the way of conclusive data.

Aside from attending to generally accepted methods of clinical research in depression—including adequate numbers, adequate trial periods, and careful distinction among phenomenologic subtypes—future studies on these substances would do well to incorporate important biochemical markers such as plasma amino acid levels, urine, and possibly CSF amine metabolites, careful control of diet, and attention to optimal levels of drug dosages.

It is possible that a subtype of depressed patient may respond to one or several of these precursors. Possibly, for some patients a combination of a 5-HT and an NE precursor may be optimal therapy. If so, it is conceivable that these agents, alone or in combination with antidepressant drugs, may enhance therapy for depression. In any case, studies designed to test out these hypotheses will clearly shed new light on the biochemistry and the pharmacotherapy of depression and of brain function in general.

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Dosage and Treatment Strategies in Schizophrenia and Affective Disorders

Chair: **Samuel Gershon, M.D.**
Department of Psychiatry
Wayne State University
Detroit, Michigan

and

Nina R. Schooler, Ph.D.
Pharmacologic and Somatic Treatments Research Branch
National Institute of Mental Health
Rockville, Maryland

Low-Dose Neuroleptics in Outpatient Schizophrenics
John Kane, Arthur Rifkin, Margaret Woerner, and Gerard Reardon
Long Island Jewish-Hillside Medical Center and Mt. Sinai Medical Center, New York, NY

Early Intervention vs Continuous Pharmacotherapy of Schizophrenia
William T. Carpenter, Jr.
Maryland Psychiatric Research Center and University of Maryland School of Medicine, Baltimore, MD

*A Strategy for Maximal Therapeutic Delivery of Antidepressants in the Context of Experimental Clinical Trials
Jan Fawcett
Rush Presbyterian-St. Luke's Medical Center, Chicago, IL

*Maintenance Drug Therapy in Depression: Current Status and Strategies
Robert F. Prien
National Institute of Mental Health, Rockville, MD

Routine Use of Psychotropic Plasma Levels in Medically Ill Psychiatric Patients
Richard Dorsey
Epp Memorial Hospital, Cincinnati, OH

*Denotes paper was presented at NCDEU meeting but not received before going to press.

Low-Dose Neuroleptics In Outpatient Schizophrenics

John M. Kane, M.D.,[2] Arthur Rifkin, M.D.,[3] Margaret Woerner, Ph.D.[2] and Gerard Reardon, M.A.[3]

Introduction

The value of maintenance neuroleptics in preventing psychotic relapse among schizophrenic outpatients has been well established. Increasing attention, however, must be given towards improving the benefit-to-risk ratio of long-term treatment. Side effects, particularly tardive dyskinesia, remain an important problem, and attempts to reduce toxicity by establishing minimum dosage requirements are necessary. No systematic dose response studies of maintenance medication is schizophrenic outpatients have been reported. In addition, there is a need for more information as to the impact of maintenance medication on patients' social and vocational adjustment and their interactions with significant others.

The present investigation was preceded by a pilot study (Kane, Rifkin, Quitkin, et al., 1979) in which the authors openly treated 57 stable or remitted patients meeting Research Diagnostic Criteria (RDC) for schizophrenia with dosages of fluphenazine decanoate (FD) ranging from 1.25 mg to 5.0 mg, administered intramuscularly (i.m.) every 2 weeks. Though relapse rates were higher than those expected with standard doses, the majority of patients were able to maintain good remission for 6 months. A subgroup of the patients who had completed 6 months of low-dose treatment were randomly assigned, double-blind, to continue on low-dose treatment or be switched to placebo. Seven of eight placebo-treated patients relapsed as compared to one of eight patients continuing on active medication ($p = .02$).

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[2] Long Island Jewish-Hillside Medical Center, Glen Oaks, NY 11004.

[3] Mount Sinai Medical Center, New York, NY 10029.

Method

This report presents preliminary results from an ongoing double-blind comparison of low dose (1.25-5.0 mg) and standard dose (12.5-50.0 mg/2 weeks) FD, conducted at three separate sites. Subjects are remitted or partially remitted RDC schizophrenics. Criteria for remission and relapse are defined in terms of Brief Psychiatric Rating Scale (BPRS) and Global Adjustment Scale (GAS) ratings. Relapsed patients are treated openly with standard doses of FD as needed (in addition to experimental medication). Following recovery from relapse, patients are continued in the study on experimental medication only. The length of the study is 1 year. Assessment measures included the BPRS every 4 weeks, the Clinical Global Improvement (CGI) every 2 weeks, and the GAS every 12 weeks. Extrapyramidal side effects and abnormal involuntary movements are assessed every 12 weeks utilizing the Simpson Angus Scale and the Simpson Dyskinesia Scale. The Premorbid Asocial Adjustment Scale is completed by the research assistant at baseline, and a modifed version of the Social Adjustment Scale is administered to the patient and a family member at baseline, Week 26, termination, and (in the case of the family assessment) at any point of relapse. The patient completes the Symptom Checklist-90 every 12 weeks. Laboratory measures include drug-free prolactin levels at baseline followed by a 2-hour prolactin response to an intramuscular injection of haloperidol. Subsequent prolactin and fluphenazine blood levels are obtained at eight additional time points during the year. The present report will not include any laboratory data.

To date, 126 patients have entered the study. Their mean age is 29 (*SD* 7.1). The mean age at first hospitalization is 23 (*SD* 5.2), and the average number of previous hospitalizations is 3.2 (*SD* 1.9). The mean number of weeks since hospital discharge is 64 (*SD* 78.5)

Results

Twenty-six of the 62 patients assigned to low-dose treatment have relapsed a total of 31 times (5 relapsed twice). Seven of these required rehospitalization. Among the 64 patients receiving

standard doses, three patients relapsed a total of four times, none requiring rehospitalization. Eighty percent of those patients relapsing on low dose did so within the first 6 months. The median length of time required to restabilize patients relapsing on low dose was 6 weeks; the mean was 11 weeks.

The results of a life-table analysis indicate that the cumulative proportion relapsing on low-dose treatment is 56%. For those patients receiving standard dose, the cumulative proportion relapsing is 7% ($p < .001$). Using the measure of relapse, the low-dose preparation is clearly not as effective as standard doses. However, there are other issues involved in assessing the risk benefit ratio. To date, four patients on standard dose and two patients on low dose have developed presumptive tardive dyskinesia. In a subgroup of 51 patients at Long Island Jewish-Hillside Hospital who completed at least 24 weeks in the study, an analysis of covariance involving the end-point Simpson Dyskinesia Scale scores revealed a significant advantage for low-dose treatment. Our preliminary analyses employing the Simpson Angus Scale for extrapyramidal side effects did not demonstrate a significant difference between the two treatment groups.

Given the relapse rates on low dose, it is important to determine the ultimate cumulative dose administered to these patients. If this proved to be equivalent to standard doses, the original goal would not be met. In a comparison of 9 low-dose patients who relapsed but completed the 1-year study with 20 patients on standard dose who completed 1 year without relapse, the low-dose patients received significantly less medication despite the relapses (16 cc's as compared to 27½ cc's in standard dose equivalents; $t = 2.39$, $p < .05$).

To assess social adjustment and family burden, interviews with the patient and separately with the family were conducted by a trained research assistant. The preliminary results from the social adjustment and family burden measures suggest that despite the increased risk of relapse, the low-dose patients are not significantly worse off than the standard dose patients and, in fact, may be doing significantly better in some areas.

Conclusion

It would appear that low-dose treatment is a viable strategy for a subgroup of remitted or partially remitted outpatient schizophrenics. Further analyses (including the laboratory data) will attempt to identify predictive factors which might help in selecting patients for whom this strategy is most likely to be effective. At present, we are left with a complex interaction of various factors which need to be taken into consideration in planning long-term treatment.

Reference

Kane, J.M., Rifkin, A., Quitkin, F. et al. Low-dose fluphenazine decanoate in maintenance treatment of schizophrenia. *Psychiatr. Res.*, 1:341,1979.

Early Intervention vs. Continuous Pharmacotherapy of Schizophrenia

William T. Carpenter, Jr., M.D.,[1] Joseph H. Stephens, M.D.,[1] Alix C. Rey, M.D.,[1] Thomas E. Hanlon, Ph.D.,[1] and Douglas W. Heinrichs, M.D.[1]

There is an increasing appreciation that long-term use of high-dose neuroleptics does not produce a generalized and continuous therapeutic effect in all schizophrenics. Neuroleptics may impair functioning in areas not affected by the illness *per se*. Also, tardive dyskinesia has become a compelling reason for avoiding indiscriminant use of neuroleptics.

The present study attempts to assess the relative merits and limitations of continuous maintenance pharmacotherapy when compared with the targeted use of neuroleptics in an early intervention strategy, followed by drug discontinuation when the patient is stabilized. The issue is not how no-drug use compares with drug use, but rather how the targeted and time-limited use of drugs compares with continuous use. The targeted alternative is, in fact, already utilized by some clinicians and viewed favorably from the perspective of long-term followup (Bleuler, 1978).

[1]Maryland Psychiatric Research Center, Box 3235, Baltimore, MD 21228.

Conceptual Model for an Early Intervention Strategy

Schizophrenia is conceptualized as a relapsing illness, and the aim of an early pharmacologic intervention is to prevent, or minimize, impending psychotic episodes. Presumably, good candidates for this approach would be robust drug responders with prodromal signs of impending relapse over a sufficient time period to permit identification and intervention. Patients who maintain insight concerning their illnesses during early phases of relapse should be more likely to seek treatment and cooperate with intervention efforts. An ongoing therapeutic relationship is crucial for the tasks of discerning prodromal signs during previous episodes, educating family and patient as to their importance in the intervention strategy, and providing a personal availability at times of impending relapse.

Methods

Patients selected for this study had recently been discharged from hospital care with a diagnosis of schizophrenia. Since one aim of the study was to characterize both good and poor candidates for a targeted drug approach, the selection of patients attempted only to assure the diagnosis of schizophrenia and the probability that patients were suitable candidates for antipsychotic medication. Patients who passed screening and agreed to participate in the treatment program were followed through an initial 4- to 8-week stabilization period in which further baseline psychiatric history, family history, and prognostic data were collected. The patient then entered a 28-day off-drug phase (42 days if withdrawal from long acting depot medication) aimed at identifying covert dyskinesia and which provided baseline assessment of psychopathology, a basis for making a diagnosis using the Research Diagnostic Criteria (RDC) and psychophysiological, neuropsychological, and biochemical data. At the end of 28 days (or sooner, if psychiatric decompensation had already required pharmacologic intervention), patients began a 2-year course of treatment with either continuous or targeted antipsychotic drug use assigned on a random basis. Subsequent interventions (increase of medication in continuous drug patients and initiation of medication in targeted drug patients) were based on a clinical judgment that prodromal symptoms had appeared and that a relapse was imminent. Drug reduction in the continuous, or drug discontinuation in the targeted groups, followed either return to baseline or stabilization of the patient's condition. All patients remained in their treatment group regardless of factors such as decompensation and rehospitalizations. Since treatment failure patients retained their original group assignment, it was possible for a patient on targeted drug treatment to remain on medication during most of the 2-year treatment course. Key points of assessment were at baseline, surrounding each decompensation, and at 6, 12, 18, and 24 months following the beginning of the experimental treatment phase. A variety of assessment techniques aimed at deficit symptoms, quality of life, role performance, and symptom course were utilized. Evaluations were made by an independent assessor free of all responsibility for clinical care.

Results

Two issues will be examined with the preliminary data from a cohort of 57 patients: consequences of drug cessation in 55 patients, and consequences of treatment assignment in the 41 patients already completing 6 months. Two of the 57 patients are excluded from the drug cessation observation. One patient was not on drugs when admitted to our clinic and one patient agreed to discontinue drugs only if returned to medication 2 weeks later. Thirty-eight of 55 patients (69%) completed 28 days off drugs without decompensation. The remaining 17 patients showed signs of relapsing and return to drugs was initiated. Four of the 17 patients required hospitalization as a result of their decompensation while off drugs. One hospitalized patient was rediagnosed manic depressive and did not return to the clinic. For the other three patients, the average hospital stay was 23 days.

The course of decompensation was charted in the 16 cases available for followup. Factor I of the Brief Psychiatric Rating Scale (BPRS) and total BPRS scores indicated that 8 patients returned to baseline levels within 2 weeks, 12 within 8 weeks, and all 16 within 12 weeks.

During the pilot phase of this project, patients

were randomized into one of the following groups: continuous drugs plus psychosocial treatment; continuous drugs without psychosocial treatment; and targeted drug with psychosocial treatment. Four patients refused their assignment to continuous drugs and were dropped from the study. Six-month followups are available on 41 patients thus far. Because there were no significant differences on primary outcome measures between the two continuous drug groups, they are combined in the Table. This Table reveals no differences between continuous and targeted drug use on several outcome measures in spite of the significantly lower exposure to drugs in the targeted group. Patients in the targeted group averaged 34% of time on drugs compared with 97% for the continuous group. Three of the 14 targeted drug patients were conspicuous failures (i.e., remained on moderate to high dose for the entire 6-month period). They were also poor outcome patients in spite of the continuous use of medication. The remaining 11 targeted drug patients averaged only 17% of time on drugs. Although the targeted group required more hospitalizations, the number is small and the difference was not statistically significant. The 14 patients in the targeted group were similar to the 27 patients on continuous drugs at 6-month followup (preliminary data at 12 months support this conclusion). Neither our clinicians' observations nor research data revealed evidence at 6-month followup that patients not receiving continuous antipsychotic drugs experienced more severe clinical or social consequences.

Conclusion

It is hoped that a 2-year treatment and observation period in a large number of cases will produce further data relevant to feasibility, prediction of response, and the impact of long-term medication on deficit symptomatology and interpersonal functioning. Present pilot data support the feasibility of the targeted drug treatment of schizophrenia and encourage an optimistic view of the potential applicability of targeted drug intervention in a sizable portion of schizophrenic patients.

Table

Outcome Variables at 6 Months in Two Drug Treatment Conditions

	Targeted Drug (N = 14)	Continuous Drug (N = 27)	P-values*
Strauss-Carpenter Outcome Score	21.5	22.9	N.S.
Global Assessment Score	52.0	54.8	N.S.
BPRS Total Score	1.93	1.75	N.S.
Number of Hospitalizations	4	2	N.S.
Days in Hospital	35	32	N.S.
Numbers of Weeks on Drugs	8.8	25.2	<.001
Total Drug Dose per Patient in CPZ Equivalents over 6 Months	28,095	69,210	<.001

*P-values based on non-paired t-tests.

Scores above are means except for number of hospitalizations.

Acknowledgment: The authors wish to thank Sue Parks who assisted in data processing and analysis.

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Routine Use of Psychotropic Plasma Levels in Medically Ill Psychiatric Patients

Richard Dorsey, M.D.,[1] and Ann Bahrani, M.D.[1]

This preliminary report covers experience gained in the routine use of psychotropic plasma level measures in medically ill psychiatric patients during calendar year 1980. All patients were hospitalized and treated on a private basis by a team com-

[1]Epp Memorial Hospital, Cincinnati, OH 45243.

prised of psychiatrists and internists. The program was conducted in an open medical setting, with major emphasis on psychopharmacology.

Our group had primary or sole responsibility for providing psychiatric services at three hospitals during the year reported. Our total admissions were 1,023, with principal psychiatric diagnoses being effective psychoses, schizophrenic disdisorders, drug/alcohol dependence, and organic brain syndrome. Patients aged 65 and over comprised about 20% of admissions and accounted for about 40% of hospital days. Ninety-five percent of geriatric patients had one or more significant medical diagnoses (e.g., arteriosclerotic heart disease, diabetes mellitus, malnutrition). Approximately 70% of nongeriatric patients had one or more significant medical diagnosis (e.g., gastrointestinal/hepatic disorders, diabetes, or arteriosclerotic heart disease).

Method

Plasma Level Measures

All specimens from our two Cincinnati hospitals were sent to National Psychopharmacology Laboratories in Knoxville, Tennessee, with our system providing 36-hour turn-around time. Our third hospital, in Columbus, Ohio, used a local reference laboratory affiliated with Ohio State University and provided 24-hour turnaround time.

Our primary Cincinnati hospital service had 619 admissions, of which 15% were geriatrics; 1215 assays were done, for an average of 1.96 assays per patient admission. Our smaller Cincinnati hospital service accounted for 162 admissions, with 65% geriatrics; assays there were 511, or 5.16 per admission. Our Columbus service, which opened in October, accounted for 242 admissions (October to December) with geriatrics comprising less than 5%. Total assays were 246, or 1.01 per patient.

Therapeutic ranges were those reported by the National Psychopharmacology Laboratory (see Table) based on published literature. Limitations of underlying evidence for some drugs were acknowledged, and ranges were regarded as useful for clinical guidance rather than as a definitive basis for dosage determination.

Table 1

Plasma and Whole Blood Assays of Psychoactive Drugs

Tricyclic Antidepressants	Therapeutic Plasma Range ng/ml	Sensitivity of the Method* ng/ml	Fee
Amitriptyline (Elavil) + Nortriptyline	125-250	5	$30
Clomipramine (Anafranil)	70-200	5	$30
Desmethylclomipramine	150-300	5	$30
Desipramine (Norpramin, Pertofrane)	40-150	5	$30
Doxepin (Sinequan) + Desmethyldoxepin	75-200	5	$30
Imipramine (Tofranil) + Desipramine (Norpramin, Petrofrane)	150-300	5	$30
Nortriptyline (Aventyl, Pamelor)	50-150	5	$30
Protriptyline (Vivactil)	50-150	5	$30

A minimum of 2 ml of plasma is required per assay for tricyclic antidepressants.

National Psychopharmacology Laboratory automatically assays the secondary amines for the tertiary tricyclics at no added cost, since interpretation without the secondary amines is not possible.

*Reporting low plasma levels is essential in distinguishing between the rapid metabolism and/or elimination versus noncompliance.

Benzodiazepines	Therapeutic Plasma Range ng/ml	Sensitivity of the Method ng/ml	Fee
Chlordiazepoxide (Librium)	400-1000	20	$22.50
Clorazepate (Tranxene) as Desmethyldiazepam	200-500	20	$22.50
Diazepam (Valium) and Desmethyldiazepam	200-400 200-500	10 20	$22.50 —
Flurazepam (Dalmane)	70-120	—	—
Lorazepam (Ativan)	Bio-availability data only	10	$22.50
Oxazepam (Serax)	200-500	20	$22.50
Prazepam (Verstran) as Desmethyldiazepam	200-500	20	$22.50

Urinary MHPG	MHPG Normal Controls		
	Males	Females	
3-methoxy-4-hydroxy phenethyleneglycol (24-hour urinary collection)	$N = 27$ 1690µg/24 hr ± 526 *(SD)*	$N = 28$ 1337µg/24 hr ± 310 *(SD)*	$45

Where the therapeutic response ranges are not given, they will be furnished in our reports.

Antipsychotics	Therapeutic Plasma Range ng/ml	Sensitivity of the Method ng/ml	Fee
*Acetophenazine (Tindal)	Bio-availability data only	0.5	$30
Butaperazine (Repoise)	100-200	2	$30
Chlorpromazine (Thorazine)	50-500	5	$30
Chlorprothixene (Taractan)	Bio-availability data only	5	$30
*Fluphenazine (Prolixin)	0.2-4	0.2	$30
*Haloperidol (Haldol)	3-15	1.0	$30
Loxapine (Loxitane)	Bio-availability data only	5	$30
Mesoridazine (Serentil)	150-1000	5	$30
*Perphenazine (Trilafon)	1-6	0.2	$30
*Piperacetazine (Quide)	Bio-availability data only	0.5	$30
Thioridazine (Mellaril)	250-1250	5	$30
*Thiothixene (Navane)	0.4-4	0.2	$30
*Trifluoperazine (Stelazine)	>4	0.2	$30

*A minimum of 5 ml of plasma is required for these antipsychotic drugs. Given sensitivities based on 5 ml of plasma.

Lithium	
Plasma Lithium	$7
RBC and Plasma Lithium and calculated RBC/ Plasma Ratio	$15

Other
Whole blood or RBC levels are assayed for the same price.

Drug levels were usually measured for psychotropic medications that patients had reportedly been taking just prior to admission. Levels for medications given in hospital were measured at about Days 5-7, and about every 5-7 days thereafter.

Clinical Utility

Our strategy for the use of psychotropic plasma levels in patient management was developed on the basis of clinical impression, without detailed data analysis. Most of our time was devoted to the patient care and administrative demands associated with establishing and running these services.

Patients found to have low psychotropic drug levels on admission were considered likely to be underdosed and/or noncompliant. Generally, the pre-admission drug was continued at a higher dose as initial treatment.

For those whose pre-admission medication produced a plasma level within the therapeutic range, we inferred that the patient was probably receiving the wrong drug. Accordingly, a different drug or class was used for initial treatment in the hospital.

High admission plasma levels suggested toxicity and/or the wrong drug (with the possible exception of a few "therapeutic window" drugs). Management in these cases consisted of initial benzodiazepine washout, followed by clinical reassessment.

After initiation of drug therapy in the hospital, plasma level guidance to dosing was used in the following way. Low plasma levels associated with poor therapeutic response justified increasing dosage on the basis of prospective benefit with minimal additional risk. Both factors were important considerations in the medically ill patient population with which we dealt.

Patients showing satisfactory therapeutic response were continued on the same medication even if the plasma levels were low, and were considered ready for discharge. Intolerance of side effects associated with low plasma level generally led us to discontinue medication.

Nongeriatric patients whose drug levels were within the appropriate range and who showed a satisfactory response were generally discharged. Geriatric patients generally were kept somewhat longer and rechecked for possible drug accumulation before being released.

A correct plasma level associated with poor therapeutic response led us to change drugs. Faced with a therapeutic level and poor side-effect tolerance, we generally tried lowering the dose, and/or blocking the most troublesome side effects. In some cases, a change of medication proved necessary.

High plasma levels associated with good therapeutic response led us to reduce the dose but con-

tinue the same medication. Generally, fewer side effects resulted, with no loss of therapeutic benefit.

High plasma level with poor therapeutic response also led us to reduce dosage. In some cases, the decrease in side effects when dosage was reduced gave us an opportunity to observe the beneficial effects of the drugs which had been masked by the side effects. In others, reduced dosage led to lowered plasma levels which had been above the therapeutic window but now fell in this range and may have contributed to a better response. Similarly, multiple side effects associated with high plasma levels were dealt with initially by reduction of dose of the same medication.

Conclusions

We found a high correlation between published therapeutic ranges and our clinical experience with patient response. Our focus was on plasma level categories of "too high," "about right," or "too low." The best correlation between plasma level and therapeutic response occurred in the sickest patients, where laboratory guidance to supplement clinical decision-making was especially desired.

In addition, we found enhanced patient satisfaction through use of laboratory testing to help establish proper treatment (an approach consistent with patient expectations from treatment in other areas of medicine). Other physicians were much more inclined to accept recommendations for high-dose psychotropic medications in medically ill patients if plasma level measurements offered reassurance concerning potential toxicity. Similarly, family physicians or outpatient psychiatrists, to whom many of our patients were referred for followup treatment, were more likely to continue therapeutic regimens with unusually high or low doses of medication when supporting plasma level data were provided. Finally, utilization review staff were impressed with the systematic approach to trying psychotropic drugs in sequence guided by plasma level measures, and would accept longer hospitalizations than otherwise would have been the case.

Overall, we believe psychotropic plasma levels constitute an extremely valuable guide to the clinician caring for the kind of patient population described. We acknowledge limitations in scientific data about the exact therapeutic range for each drug, but believe that even crude laboratory guidance is far superior to none at all. Based on our experience to date, we believe routine use of psychotropic plasma levels helps to maximize therapeutic benefit while minimizing risk and side effects for the medically ill psychiatric patient.

Assessing the Effects of Electroconvulsive Therapy (ECT)

Chair: **Richard D. Weiner, M.D.**
Department of Psychiatry
VA Hospital
Durham, North Carolina

and

Jack D. Blaine, M.D.
Pharmacologic and Somatic Treatments Research Branch
National Institute of Mental Health
Rockville, Maryland

Critical Research Issues in Assessing the Effects of ECT
Jack Blaine
National Institute of Mental Health, Rockville, MD

Evaluation of the Central Nervous System Risks of ECT
Richard D. Weiner, Helen Rogers, and Jonathan Davidson
Duke University Medical Center and VA Hospital, Durham, NC

Efficacy of ECT in the Treatment of Depression: Wave Form and Electrode Placement Considerations
Charles A. Welch, Douglas Weir, Jane F. Cahill, and Michel R. Mandel
Massachusetts General Hospital and Harvard Medical School, Boston, MA

ECT Combined with Neuroleptics in the Treatment of Schizophrenia
Joyce G. Small, Victor Milstein, Marietta H. Klapper, Jeffrey J. Kellams, and Iver S. Small
Larue D. Carter Memorial Hospital and Indiana University School of Medicine, Indianapolis, IN

Critical Research Issues

Jack D. Blaine, M.D.[1]

The inclusion of a session on ECT in the New Clinical Drug Evaluation Unit (NCDEU) meeting program reflects the new responsibility for research on somatic treatments including ECT, given the Pharmacologic and Somatic Treatments Research Branch as a result of the Fall 1980 reorganization of the Division of Extramural Research Programs of the National Institute of Mental Health. Therefore, the Branch intends to develop a program of research support of ECT projects assessing the effects and role of ECT in the treatment of the mentally ill. In this session, the panel will discuss some of the critical research issues in the ECT field and report data from several of the ongoing clinical ECT research studies.

ECT was first introduced into clinical psychiatry over 45 years ago. Seizures modified by anesthesia and muscle paralysis have been commonly used for over 30 years. Despite this extensive clinical experience, ECT remains a controversial treatment among both mental health professionals and the general public. Much of this

[1]National Institute of Mental Health, Rockville, MD 20857.

controversy arises from emotionally laden concerns including those about irreparable brain damage and abuses of patients' rights. These fears and concerns are elicited by the images of ECT treatment itself in contrast to more graphically benign psychotherapy or pharmacotherapy.

The controversy also exists in part because of a paucity of studies meeting contemporary scientific standards. ECT was developed and accepted as an effective treatment prior to the psychopharmacologic agents, and prior to the advent of the controlled clinical trial methodologies devised to assess the safety and efficacy of drugs. In addition, the complexity of the ECT treatment procedures and processes, in contrast to swallowing a pill, complicates the feasibility of carrying out well-controlled clinical ECT trials. For example, the inclusion of a "placebo" or simulated sham ECT control group raises ethical concerns. This design exposes severely ill patients to the potential risks of general anesthesia and muscle paralysis without probable therapeutic benefits. Because most patients referred for ECT are severely ill and often are not responsive to ongoing pharmacotherapy and psychotherapy, avoiding subject selection bias poses significant additional difficulties for the design of ECT studies, especially those comparing ECT to other therapies. Also, the side effects of confusion and memory loss potentially disrupt the blind status of the subjects, treatment staff, and raters. These are but a few of the critical design issues which need to be addressed and solved.

Fortunately, interest in ECT research has increased in recent years. As a result, increasing numbers of studies are being done using contemporary scientific designs and methodologies. The findings from several recent sham-controlled studies done in England demonstrate the effectiveness and safety of ECT as a treatment of endogenous depression (Freeman et al., 1978; Johnstone et al., 1980; West, 1981). Together with Ottosson's sophisticated series of studies in Sweden in the late 1950s, they demonstrate that the occurrence of a generalized central nervous system seizure is the essential therapeutic component. Further, the intensity of the electrical current inducing the seizure appears not to be related to therapeutic effect, but seems directly related to the primary side effects of ECT, post-ECT confusion, and memory impairment (Ottosson, 1960).

Therefore, research effort is being directed at more sophisticated issues than primary efficacy and safety. Considerable research effort is focusing on the nature, extent, and duration of the ECT-induced impairment in memory and other cognitive functions. The differential outcome of ECT techniques utilizing various electrical stimuli (brief pulse vs sine wave current) and electrode placements (unilateral nondominant vs bilateral position) is being assessed in terms of the side effects of memory and other cognitive function impairments as well as the therapeutic effect on depressive affect.

The following two papers by R. Weiner and C. Welch and their colleagues will focus on these issues. The final paper, by J. Small, will address aspects of two other critical issues in the efficacy area. The first issue is clinical indications for ECT. The second issue is the safety and efficacy of ECT compared to and combined with drugs. Dr. Small's presentation will present data on the combined use of ECT and neuroleptics in the treatment of schizophrenia. However, the question of safety and efficacy of ECT compared to and combined with optimal antidepressant therapy in the treatment of acute depression remains to be definitively answered.

While most endogenously depressed patients respond to pharmacotherapy, significant numbers of nonresponders are successfully treated with subsequent ECT (Paul et al., 1981). Clinical reviews also indicate the superior effectiveness of ECT for patients unable to take adequate doses of antidepressants for medical reasons (e.g., the elderly or patients with cardiac disease), and superior effectiveness for delusional or catatonic patients, and for severely ill suicidal or cachetic patients requiring a rapid response (APA, 1978; Fink, 1979). Thus, a critical area requiring investigation appears to be delineation and the definitive testing of clinical predictors or historical indicators for selecting ECT vs antidepressant medication as a first-line treatment for endogenous depression.

Finally, recent studies have shown that many patients who recover from an acute episode of major depression, whether treated with ECT or tricyclic antidepressants, have chronic course or become symptomatic again (Prien, 1981). Thus, the effectiveness of ECT, compared to and combined with antidepressants in preventing relapse

or recurrences of new depressive episodes, requires investigation. Hopefully, the recent availability of potential biological markers of endogenous depression (e.g., dexamethasone suppression test, sleep electroencephalography (EEG) abnormalities) and techniques reassessing the adequacy of therapy (e.g., tricyclic antidepressant plasma levels, seizure time, and EEG changes with ECT) will facilitate the performance of definitive studies in these important areas.

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Evaluation of the Central Nervous System Risks of ECT

Richard D. Weiner, M.D., Ph.D.,[1,2] Helen J. Rogers, Ph.D.,[2] Jonathan Davidson, M.B., M.R.C. Psych.,[2,3] and Robert D. Miller, M.D., Ph.D.[2,3]

[1]Psychiatry Service, Durham VA Medical Center, Durham, NC 27705.

[2]Department of Psychiatry, Duke University Medical Center, Durham, NC 27710.

[3]John Umstead State Hospital, Butner, NC 27059.

Introduction

Electroconvulsive therapy (ECT) is currently used as a treatment modality for severely ill psychiatric patients, particularly for major depressive disorders (Weiner, 1979). There continues to be controversy, however, with respect to ECT's risk/benefit considerations, a situation which is confounded by the widely varying types of ECT in use today, particularly in terms of electrode placement and stimulus waveform.

To help resolve this matter, a controlled prospective clinical study has been set up to investigate the acute and long-term effects of ECT upon memory, the electroencephalogram (EEG), and clinical status. In particular, this study considers the differential effects of stimulus electrode placement and stimulus waveform. As this is an ongoing study now in its third year, data collection and analysis have not been completed and only salient features of the data regarding the acute effects of ECT upon certain memory and EEG parameters will be presented here. Preliminary data regarding therapeutic response are reported elsewhere (Welch, Weiner, Weir, Cahill, Rogers, Davidson, Miller, & Mandel, 1981).

Methods

Experimental subjects have been referred for voluntary ECT treatment by their psychiatrists. All of those who meet Research Diagnostic Criteria (Spitzer, Endicott, & Robins, 1978) for major depressive disorder and have no evidence of preexisting central nervous system (CNS) impairment are subjected to a full series of test measures (memory, EEG, and clinical). ECT subjects who do not meet these criteria are tested only in terms of EEG. Control subjects meet all study criteria except for not being referred for ECT. Memory data will be presented on 33 experimental and 8 control subjects, while EEG data is presented on 40 experimental and 4 control subjects.

All experimental (ECT) subjects are randomly assigned to either unilateral nondominant or bilateral electrode placement and either sine wave or bipolar pulse stimuli. Standard modified ECT procedures are otherwise carried out, with the addition of EEG and stimulus energy monitoring.

The number of ECT treatments is determined by the subject's psychiatrist on a clinical basis. No significant difference in age, sex, education, I.Q., or socioeconomic status among the various treatment groups was noted.

All testing is done prior to ECT, 2-3 days post completion of the treatments, and 6 months later (only the acute data will be presented here). Clinical measures have been discussed in part elsewhere (Welch et al., 1981). Memory measures include a variety of tests of anterograde and retrograde memory performance (for both dominant and nondominant hemispheric function). The personal, or autobiographic memory questionnaire focuses upon specific events relating to the subject's own life, particularly over the past year. A time frame which appears to be especially sensitive (Squire, Slater, & Miller, 1981) will serve as the memory measure presented below. In terms of physiologic abnormalities (Small, Small, & Milstein, 1978), both visual rating of EEG slowing and computer spectral analysis are utilized, with data from the latter being presented here. Testing is done blind with respect to subject group assignment, as indicated.

Results

The fraction of baseline personal memory items not remembered at the second testing session (2-3 days post completion for ECT experimental subjects) is shown in Figure 1. Analysis of variance shows control subjects to be *less* amnestic than ECT subjects ($p \leq .001$), and unilaterally treated subjects to be *less* amnestic than those receiving bilateral treatment ($p \leq .01$). A small trend for sine wave-treated subjects to be more impaired than those treated with pulse stimuli did not reach clinical significance ($p \leq .08$). Further statistical investigations revealed that the degree of apparent amnesia was *not* correlated with mean seizure length or total seizure duration, but *was* positively correlated with number of treatments ($p \leq .03$).

The difference in EEG slowing between the second testing session (2-3 days post completion of ECT for the experimental subjects) and the baseline measurements is shown in Figure 2. Analysis of variance shows control subjects to exhibit *less* slowing than ECT subjects ($p \leq .05$). Also, unilaterally treated subjects show *less* slowing than bilaterally treated subjects ($p \leq .02$). An additional finding, different from the memory results, is that subjects receiving pulse ECT show significantly *less* slowing than subjects receiving sine wave administration ($p \leq .01$).

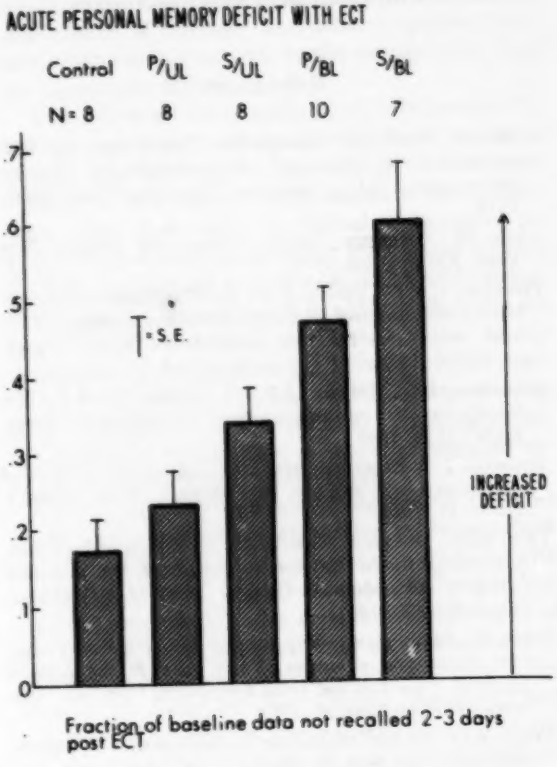

FIGURE 1

Discussion and Conclusion

The above findings indicate that the use of personal memory questionnaires and computerized EEG spectral analytic techniques can be used to extend the sensitivity of the assessment of CNS impairment following ECT. Acute personal memory impairment is less with unilateral nondominant electrode placement, as reported by

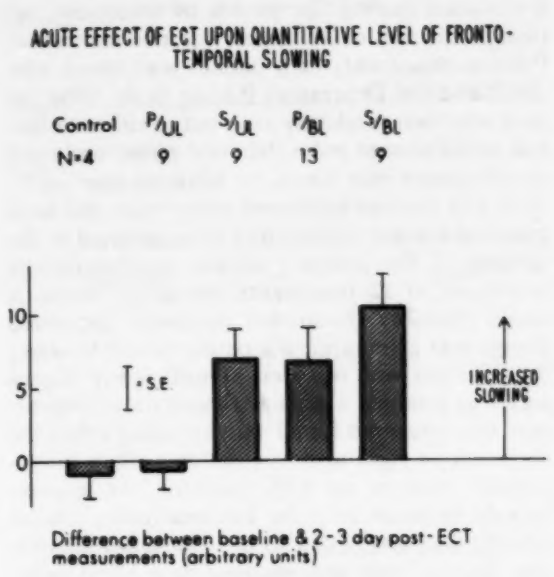

FIGURE 2

many others (e.g., Squire, 1977). No clear effect of stimulus waveform upon acute memory deficits is apparent, though a possible mild dysmnestic effect of sine wave stimuli requires further evaluation. In addition, the number of treatments, but not seizure duration, was found to exert a cumulative effect upon acute memory impairment, suggesting that, in general, brief electrically induced seizures appear to exert discrete effects upon memory performance.

In terms of acute EEG changes, unilateral nondominant ECT results in less slowing than bilateral ECT, while pulse ECT results in less slowing than sine wave ECT. This indicates that EEG slowing, which appears more sensitive to stimulus waveform than does amnesia, may represent a somewhat different phenomenon than amnesia, with the former being a nonspecific encephalopathic change, perhaps related to confusion, and the latter being a more specific effect of ECT, perhaps mediated through temporal lobe mechanisms.

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Efficacy of ECT in the Treatment of Depression: Wave Form and Electrode Placement Considerations

Charles A. Welch, M.D.,[1] Richard D. Weiner, M.D.[2,3] Douglas Weir, M.D.,[1] Jane F. Cahill, R.N.M.S.,[1] Helen J. Rogers, Ph.D.,[2] Jonathan Davidson, M.B., M.R.C. Psych.[4] Robert D. Miller, M.D., Ph.D.,[2] and Michel R. Mandel, M.D.[4]

There is wide variation in electroconvulsive therapy (ECT) technique and little data to indicate which technique, if any, is must efficacious. The two most important variables are the position of the treatment electrodes on the head, and the shape of the electrical wave form. Many clinicians have strong opinions about the effect of these variables on efficacy, but studies to date have been inconclusive.

Bilateral fronto-temporal electrode placement is still the standard technique in this country, in spite of an increasing body of evidence that unilateral nondominant placement has less side effects (d'Elia, 1970; Squire, 1977) and that it may be equally efficacious (d'Elia & Raotma, 1975). Although existing studies vary widely in methodology, more rigorously designed studies tend to show equal efficacy, while those lacking control

[1]Somatic Therapies Consultation Service, Massachusetts General Hospital, Boston, MA 02124.
[2]Department of Psychiatry, Duke University Medical Center, Durham, NC 27705.
[3]Durham VA Medical Center, Durham, NC 27705.
[4]Umstead State Hospital, Butner, NC 27059

groups, blind raters, objective treatment criteria, or other important design features tend to show a differential in efficacy favoring bilateral.

Stimulus wave form has also been studied with respect to efficacy. Again, wide variations in methodology make it difficult to draw firm conclusions from the published studies. In the seven comparisons between sine wave and brief pulse performed since 1944, methodology varied widely, but several trends do emerge from this data (Weaver, Ives, Williams, & Nies, 1977; Weiner, 1980). In all but one study, sinusoidal and pulse wave forms were found to be equal in their ability to produce satisfactory seizures. Furthermore, pulse stimulation required less total energy to trigger a seizure, generally 50% or less than the energy required for sine wave stimulation. Clinical efficacy was found to be equal in all but one study, in which sine wave was found to be slightly more effective.

Unfortunately, a variety of different stimulus doses and electrode placements were used in these studies, and a clear comparison of wave forms, free of other variables, cannot be made. Furthermore, there has been no therapeutic comparison of wave forms using the vertex-temporal placement technique as described by d'Elia (1970). This placement requires less energy than the bilateral or other unilateral placements (Erman, Welch, & Mandel, 1979), appears to be equally efficacious, and is therefore clearly deserving of further study.

Because of the foregoing methodological problems, the present study was initiated with the intent to control simultaneously for variables of wave form and electrode placement. The objectives are to assess the previous findings: That unilateral ECT may be as effective clinically as bilateral ECT, and that brief pulse stimulus is as effective as sine wave stimulus.

Method

Patients in the study were referred for ECT on the basis of clinical indications, and most were resistant or intolerant to antidepressant medications. They were required to fit the Diagnostic Statistical Manual-III (DSM-III) criteria for major depressive episode with melancholia, and to have no evidence of preexisting cognitive impairment other than that consistent with depressive illness. All patients were free of antidepressant medication during the course of treatment, although the use of sedatives was not controlled. Prior to treatment, each patient was tested with the Hamilton Depression Rating Scale. The patient was then randomly assigned to either unilateral nondominant pulse, bilateral pulse, unilateral nondominant sine wave, or bilateral sine wave. ECT was then administered every other day until maximal clinical efficacy had been attained in the opinion of the primary clinical psychiatrist. A maximum of 12 treatments was given within a single modality. Estimated minimum threshold dosage was given and, if a patient failed to seize, the stimulus was repeated at sufficiently higher joules to produce a seizure. Duration of convulsion was measured for all patients using either the occlusion of right-arm circulation with a blood-pressure cuff or an EEG monitor. At approximately 48 hours after the last treatment, clinical efficacy was assessed with the Hamilton Depression Rating Scale administered by a blind rater. Efficacy was measured as reduction in raw Hamilton score from pretreatment testing to the score at 48 hours after the last treatment.

Results

Figure 1 compares the degree of improvement for each cell, and Figures 2 and 3 compare patients by electrode placement and wave form, respectively. Figure 1 indicates that the two unilateral cells had greatest mean improvement. Figure 2 shows a superiority of unilateral ECT over bilateral ECT that is statistically significant at the $\leq .05$ level. When the two centers are analyzed separately, the Duke data continue to show a statistically significant difference, while the Massachusetts General Hospital data show a trend in the same direction, although it is not statistically significant. Figure 3 indicates no significant difference in efficacy between the two wave forms.

FOUR CELL COMPARISON
DUKE AND MGH COMBINED

GROUP		N	MEAN REDUCTION IN HAMILTON SCORE
PULSE	UNILATERAL	12	33.50
	BILATERAL	18	25.28
SINE	UNILATERAL	17	36.35
	BILATERAL	12	25.00

Figure 1

COMPARISON OF ELECTRODE PLACEMENT
DUKE AND MGH COMBINED

GROUP	N	MEAN REDUCTION IN HAMILTON SCORE
UNILATERAL	29	35.17
BILATERAL	30	25.17

Figure 2

COMPARISON OF WAVE FORM
DUKE AND MGH COMBINED

GROUP	N	MEAN REDUCTION IN HAMILTON SCORE
PULSE	30	28.57
SINE	29	31.66

Figure 3

Discussion

The finding that sine wave and brief pulse stimulus appear equally efficacious is not surprising in the light of previous research. Ottosson's (1960) milestone work indicated that a generalized grand mal seizure is the essential component of the treatment and that other variables such as mode of stimulus and severity of side effects were unrelated to ultimate efficacy. Subsequent clinical comparisons of wave form have continued to support the contention that how you trigger a seizure is unrelated to efficacy, but whether or not you trigger a seizure is related to efficacy.

The findings on electrode placement are somewhat more surprising. Although a number of investigators have found unilateral electrode placement to be just as efficacious as bilateral, this is the first randomly assigned prospective trial to find a greater efficacy associated with unilateral placement. The investigators' interpretation of these findings is that the bilateral group appeared less improved because of the greater cognitive side effects associated with that treatment at the time of measurement. It is possible that these placements are equally efficacious when the artifact of cognitive side effect is removed and this view, again, would be consistent with the work of Ottosson (1960) regarding the importance of the seizure itself.

While the investigators feel that it is premature to draw firm conclusions from their data until the study is completed, they also feel that the trends from this preliminary analysis are unlikely to change significantly as the study proceeds. The clinical importance of these findings is that there is probably at least equal efficacy with unilateral and pulse techniques in addition to markedly reduced side effects, compared with bilateral sine wave treatment.

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ECT Combined with Neuroleptics in the Treatment of Schizophrenia[1]

Joyce G. Small, M.D.,[2] Victor Milstein, Ph.D.,[2] Marietta Klapper, M.S.,[2] Jeffrey J. Kellams, M.D.,[2] and Iver F. Small, M.D.[2]

The purpose of the present study was to assess the relative efficacy of neuroleptics combined with electroconvulsive therapy (ECT) compared with neuroleptics alone in the treatment of schizophrenia. Study patients met criteria (Feighner, Robins, Guze, & Woodruff, 1972) for schizophrenia. The design included randomization of treatment, placebo controls, a modified double-blind design, and short- and long-term followup. The majority of patients were assigned to treatment either with thiothixene hydrochloride or thiothixene combined with ECT. Fewer patients were assigned to placebo combined with ECT and still fewer to placebo alone. Nondominant unilateral ECT was employed with electroencephalographic monitoring to assure that major generalized seizures were induced. A standard rating scale battery (Levine, 1979) plus the Emotional Blunting Scale (EBS) (Abrams & Taylor, 1978) were employed. The Halstead-Reitan-Wepman Neuropsychological test battery (Reitan, 1966) was utilized for evaluation of cognitive impairment. Dosage of drugs and number of ECT were individualized, but a lower limit of 12 treatments for an ECT regimen was imposed. Video-taped samples of interview behavior were obtained for time-blind psychiatric ratings (Renfordt & Busch, 1976). Patients were assessed biweekly for the first 2 weeks and weekly thereafter for 6 weeks with followup at 6 and 12 months. Patients were maintained in the initially assigned treatment groups for as long as possible but were dropped because of patient refusal to continue, clinical deterioration, uncontrollable side effects, or insufficient therapeutic response. Treatment related dropouts were not replaced and were included in the statistical analyses by substitution of last active scores for missed evaluation points.

Seventy-five patients were enrolled in the study and randomly assigned to treatment. There were no differences between the treatment groups in terms of age, sex, education, duration of illness, nor in the pretreatment assessments of psychopathology.

Survival time on the study was one of the dependent variables examined. Patients on placebo, and placebo combined with ECT were dropped from the study significantly sooner than the others on an average of 11 and 19 days, respectively. Mean survival time was 46 days for thiothixene-ECT and 60 days for thiothixene. The difference between the latter two was not statistically significant. Reasons for study termination were similar in the four treatment groups. The only difference was that compliance with taking medications was better in the ECT-treated patients.

There were no significant differences in doses of neuroleptics or corresponding amounts of placebo in the three active treatment groups. More anticholinergic agents were used in the patients treated with thiothixene alone. The two ECT groups received a series of 15 treatments on the average. The seizures were shorter in the thiothixene-ECT combined group than in the patients on placebo with ECT, 37 seconds compared to 43 seconds.

Neuropsychological test data revealed no group differences before treatment. Afterwards there were indications of greater impairment of performance in the thiothixene—ECT group in comparison with performance of patients receiving

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[2]Indiana University School of Medicine, Larue D. Carter Memorial Hospital, Indianapolis, IN 46202.

placebo—ECT. This was true for tests involving right, left, or both hemispheres. Dosage of neuroleptic or anticholinergic medication was not associated with impaired test performance.

Two-way analysis of variance for repeated measures of the four treatment groups over the nine assessment periods yielded significant treatment group and time effects with no significant interactions. On the Clinical Global Impression Scale the majority of significant differences favored the thiothixene-ECT combined group in comparison to the placebo-ECT and placebo reference conditions. There were no statistically significant differences between the two groups receiving active drug. The Brief Psychiatric Rating Scale (BPRS) discriminated between the thiothixene patients and those treated with placebo-ECT or placebo, favoring the former on factors of thinking disturbance and anxiety-depression. The drug-ECT combination group did best in areas assessed by the EBS. The Abnormal Involuntary Movement Scale (AIMS) indicated that patients given neuroleptics alone had more orofacial movements than the other treatment groups.

The overall conclusion was that thiothixene alone and thiothixene combined with ECT are both effective treatments of exacerbations of schizophrenia as compared to the reference groups which received placebo and unlateral ECT or placebo alone. The course of treatment with thiothixene-ECT was smoother, with fewer problems with drug compliance, less apathy, withdrawal and indifference, fewer movement disorders, and other side effects as well as overall better global improvement and therapeutic efficacy. There were no differences in survival time on the study, duration of hospitalization, or disposition on discharge, but family adjustment in those patients living at home was significantly better in the ECT-combined group than for those who received neuroleptics alone. There was more impairment in neuropsychological test performance with drug-ECT combined than with ECT without active drugs, and seizures were shorter, although these differences may not by clinically important. Neuroleptics alone were more effective in controlling signs and symptoms assessed by BPRS factors of thinking disturbance and anxiety and depression.

The conclusion is that neuroleptics combined with ECT and neuroleptics alone are useful therapeutic interventions in schizophrenia, each with a somewhat different symptomatic profile. Projected followup investigations may determine whether or not there are long-range advantages to either form of treatment.

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Current Issues in the Treatment of Anxiety States and Disorders

Chair: **Karl Rickels, M.D.**
Department of Psychiatry
University of Pennsylvania
Philadelphia, Pennsylvania

and

Allen Raskin, Ph.D.
National Institute of Mental Health
Rockville, Maryland

*Imipramine Treatment for Primarily Anxious Outpatients
Ronald S. Lipman
National Institute of Mental Health
Rockville, MD

Predictability of Treatment Reponse of Diazepam at Several Points During the Course of a 6-Week Drug Trial
Robert W. Downing
University of Pennsylvania, Philadelphia, PA

Issues in Long-Term Treatment with Diazepam
Karl Rickels
University of Pennsylvania, Philadelphia, PA

*Pharmacological Dissection of Anxiety
Donald F. Klein
New York State Psychiatric Institute and Columbia University, New York, NY

*Agoraphobics' Response to Imipramine and Chlordiazepoxide
Douglas M. McNair
Boston University, Boston, MA

Behavioral Assessment of Drug Effects in Obsessive-Compulsive Disorder
Samuel M. Turner
Western Psychiatric Institute and Clinic, Pittsburgh, PA

*Denotes paper was presented at NCDEU meeting but not received before going to press.

Predictability of Treatment to Response to Diazepam at Several Points During the Course of a 6-Week Drug Trial[1]

Robert W. Downing, Ph.D.,[2] and Karl Rickels, M.D.[2]

Among the aims of a recently completed large-scale study of diazepam treatment in patients suffering from chronic anxiety is the determination of predictors of response to both an acute (6 weeks) and a maintenance (6 months) treatment phase of the trial. The present report deals with a preliminary investigation of the predictability of treatment response at several points during the course of the acute phase of the study (after a 1-week placebo washout period, and after 2, 4, and 6 weeks of treatment with diazepam). It is also concerned with the contributions to predictability made at each of these points by each member of a small set of predictors, selected either on the basis of the predictive role they have played in previous studies (age, social class, presence or absence of previous treatment, and the severity of initial anxiety and initial depression), or because of theoretical considerations (Eysenck Neuroticism and Precipitating Stress).

Of the 133 primarily anxious, nonpsychotic outpatients included in the present investigation, 59% were female, 81% white, and 62% married. Mean age was 42.7 ± 12.6 years. Class IV formed the modal socioeconomic level (47%), but the remaining classes were well represented (I-II, 12%; III, 23%; V, 18%). In terms of illness-related factors, 38% of the group had been ill for 3 or more years; 62%, for 1 or more years. Seventy percent of the sample had received previous treatment for emotional problems. Mean score on the Covi Anxiety Screen was 10.4 ± 1.7, and on the Raskin Depression Screen, 6.8 ± 1.83. Precipitating stress was reported for 50% of the group.

The seven independent variables listed in the Table were employed as regressors in a standard multiple regression procedure to assess the predictability of 7-point scale physician ratings of Global Improvement (1 = very much better, 7 = very much worse) after the 1-week placebo washout period and after 2, 4, and 6 weeks of treatment with diazepam (20-40 mg/d). In addition to the multiple R's and R^2's obtained at each time period, the Table includes the partial r of each regressor with improvement. The signs of each partial r have been adjusted so that the indicated class (e.g.; Previous Treatment: Yes) or dimensional extreme (e.g.; Eysenck Neuroticism: High) are associated with greater improvement when r is positive and with lesser improvement when r is negative for that variable.

Table

Predictors of Physician Rated Global Improvement After a 1-Week Placebo Washout and After 2, 4, and 6 Weeks of Treatment With Diazepam for 113 Anxious Patients

	Placebo	Diazepam Week 2	Diazepam Week 4	Diazepam Week 6
	r_p	r_p	r_p	r_p
Age: Old	00	13	02	06
Previous Treatment: Yes	-16†	-18*	-21*	-30§
Neuroticism: High	-15†	-18*	-14	-19*
Social Class: High	03	21*	22**	11
Precipitating Stress: Yes	16†	06	22**	20*
Covi Anxiety: High	26**	-04	06	02
Raskin Depression: High	-06	-04	-24**	-12
	R	.38	.35	.43	.41
	R^2	.141	.122	.188	.167
	P	.007	.02	.0005	.004

* p .05
** p .01
† p .10
§ p .001

The percentage of predicted variance ranges from 12.2% at 2 weeks to 18.8% at 4 weeks. An examination of the R's and R^2's across the four points at which they are assessed provides no evidence of a reliable shift in predictability between the first and seventh weeks of treatment. Predictability after 6 weeks of diazepam treatment is at least as high as it is at any of the previous assessment points. The temporal configuration of the contributions made to predictability, how-

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[2]Psychopharmacology Research and Treatment Unit and the Private Practice Research Group, Department of Psychiatry, University of Pennsylvania, Philadelphia, PA 19104.

ever, varies widely across the set of independent variables employed. Patient age, despite its implications for the kinetics of benzodiazepine metabolism and its putative role as at least a rough indicator of physical, psychological, and social functioning remains uniformly unrelated to treatment response. In contrast, the contribution made by the presence/absence of previous treatment for emotional problems shows a monotonic increase across assessment periods with those patients who have sought previous treatment manifesting the least improvement. The presence of a condition requiring further treatment after previous treatment was obtained would appear to impose tangible limits upon the capacity for treatment response; this factor accounts for 9% of treatment response after 6 weeks of diazepam treatment.

Higher scores on the Eysenck Neuroticism scale manifest a modest, but consistently negative impact upon treatment response across all assessment periods. This purported measure of potential for neurotic functioning emerges as sufficiently independent of the predictive impact of presently anxious and depressive symptomatology to make a significant contribution ($p < .05$) after 2 and after 6 weeks of diazepam treatment. Higher socioeconomic class affiliation has a positive implication for response to active drug but not to placebo, while the occurrence of precipitating stress implies more adequate response to both placebo ($p < .10$) and to active drug. More severe presenting anxiety (Covi Screen) is associated with greater response during the placebo washout period but is unrelated to subsequent drug response. More severe presenting depression (Raskin Screen) has negative implications for drug response which are statistically significant at only the 4-week point. Generally, it may be concluded that more adequate treatment response is experienced by those individuals with greater material, personal and social resources supportive of adequate functioning.

Issues in Long-Term Treatment with Diazepam[1]

Karl Rickels, M.D.,[2] W. George Case, M.D.,[2] and Robert W. Downing, Ph.D.[2]

A diazepam maintenance drug trial, initiated several years ago, is presently in its last study phase and all patients have been entered into the trial. This report is based on completed patient data available as of April 1981.

The acute single-blind study phase called for a 1-week placebo washout period and a 6-week active drug treatment period where diazepam was prescribed in daily dosages ranging from 20-40 mg with an average dose of 25 mg/day. Improved patients or patients hoping to derive more benefit through longer diazepam treatment then entered an 18-week double-blind maintenance phase.

One-third of all patients entering the maintenance phase were switched to placebo at the onset, one-third after 8 weeks in the maintenance phase, i.e., after a total diazepam period of 14 weeks, and one-third of patients after 16 weeks in the maintenance phase or a total number of 22 weeks on diazepam. For all patients completing 22 weeks of diazepam treatment, two additional placebo weeks with weekly visits were added. Followups were conducted 3 and 12 months after the patient completed the maintenance phase.

Only chronically anxious, nonpsychotic patients of both sexes between 18 and 65 years of age who were anxious for at least 3 months, and whose mean chronicity was more than 1 year, were initiated into the study. Their initial Covi Anxiety score was at least 8 and their Hamilton Anxiety score at least 18. Of more than 350 anxious patients entering the placebo washout period, 158 patients so far have completed the maintenance phase, either by completing all 24 weeks of the program or by dropping out earlier for various reasons (e.g., return of symptoms or withdrawal reaction).

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[2]Department of Psychiatry, University of Pennsylvania, Philadelphia, PA 19104.

The following preliminary findings have been obtained so far:

1) Clinical improvement observed during the first week of diazepam treatment was a highly significant predictor of a 6-week diazepam treatment response ($p < .001$), with almost 90% of patients reporting "much or very much" improvement after only 1 week of treatment being markedly improved after 6 weeks of treatment. The representative improvement percentage for patients reporting at 1 week only minimal improvement is 45%, and for patients reporting no improvement or getting worse after 1 week is 20%.
2) No tolerance to the diazepam effect developed in improved patients over the total 22 weeks of diazepam treatment.
3) Patients experienced maximal improvement during the initial 6 weeks of treatment, and no additional improvement could be produced in any patient during the entire maintenance phase, even when dosages were increased to a daily maximum of 40 mg/day.
4) Return of symptoms after an abrupt change from diazepam to placebo after 6 weeks of diazepam treatment occurred in 45% of all patients. In those patients who continued 22 weeks on diazepam, the return of symptom rate was reduced to 25%. Thus, about 55% of chronically anxious patients with a mean chronicity of more than 1 year needed only 6 weeks of diazepam treatment to become symptom free and to maintain this freedom for at least several months while on placebo medication.
5) Withdrawal reactions were reported by 20 out of 158 patients (13%). Two withdrawal reactions occurred in patients who were on diazepam for only 6 weeks, ten in patients who were on diazepam for 14 weeks, and eight in patients who were on medication for 22 weeks. Seven of these 20 patients had only very transient reactions that lasted for only a few days and had disappeared 1 week later. Some of these patients reported temporary sleep problems and one patient stated that he felt slightly anxious for 3 days, similar to when he stopped smoking. The withdrawal reaction in the remaining 13 patients were clear withdrawal reactions which occurred within 2-3 days after abrupt diazepam withdrawal and shift to placebo; these symptoms peaked during Days 5 to 7 and disappeared with or without treatment within a few weeks, as was recently reported by Winokur et al. (1). Table 1 summarizes those withdrawal reactions reported by most of the 13 patients.

Table 1

Diazepam Withdrawal Symptoms

Extreme Distress
GI Symptoms (Nausea, Diarrhea, or Constipation)
Diaphoresis
Tremor
Lethargy
Dizziness
Increased Acuity for Sound and Smell
Restlessness
Insomnia
Tinnitus
Feelings of Depersonalization
Difficulties Expressing Thoughts Coherently
Headaches
Irritability
Anxiety
No Convulsions
No Psychotic Reactions

Further examination of our data made it quite clear that withdrawal response could not be looked at only as a function of study medication but had to be viewed in the context of medication taken prior to entering the 1-week placebo washout period. In fact, close inspection of prior drug treatment data indicated that 4 of the 13 patients with clear withdrawal reactions should never have entered our study, since they demonstrated existing clear-cut withdrawal reaction during the placebo washout period. Incidences of withdrawal reactions, irrespective of whether they were mild or severe, are given in Table 2 as a function of total consecutive prior sedative-benzodiazepine intake. Table 2 indicates clearly that chances to develop withdrawal reactions to an abrupt withdrawal of diazepam used in medically acceptable daily dosages of 15-40 mg increases with length of prior sedative treatment. No withdrawal reactions were seen prior to 14 weeks of benzodiazepine treatment; the two withdrawal reactions occurring after 6 weeks of study medica-

tion occurred in patients who had been on long-term benzodiazepine use and in fact had already had a withdrawal reaction during the placebo washout period. The three patients who developed clear-cut withdrawal reactions after only 14 weeks of diazepam and without a history of prior sedative drug use were heavy social drinkers, and the question at least should be raised whether this drinking habit may have contributed to the occurrence of withdrawal symptoms.

Table 2

Withdrawal Reactions After Abrupt Discontinuation of Diazepam Treatment as Function of Prior Sedative Drug Use*

	No Withdrawal	Withdrawal
No Prior Sedative	83	6 (7%)
Prior Sedative < 8 Months' Duration	38	3 (7%)
Prior Sedative ≥ 8 Months' Duration	17	11 (39%)

$\chi^2 = 21.83$; $N = 138$
* Patients who terminated on diazepam are counted as "No Withdrawal."

6) Major factors found to contribute to diazepam withdrawal are the following: a) abrupt discontinuation of treatment; b) continuous treatment for at least 4 months' duration in therapeutic dosages; c) the longer the treatment duration with a sedative-benzodiazepine, the higher the chance of withdrawal reactions to occur even in therapeutic dosage; d) however, since many patients with years on benzodiazepine medication did not develop withdrawal reactions in our study, other as yet unknown factors need to be determined.
7) The time course of withdrawal reactions produced by abrupt benzodiazepine discontinuation indicates a swift development of symptoms, peaking after 5 to 7 days and slowly receding over the next 2 to 4 weeks. These symptoms are frequently not only different from the symptom the patient originally had, but also much more disturbing. However, many patients experience only very mild symptoms, lasting only a few days. In contrast, return of symptoms shows a much different time course. Symptoms usually develop over 2 to 4 weeks and once they are fully developed do not disappear without additional treatment. The symptoms also are usually of the same type as the patient's original symptoms and they are generally of less severity and never of more intensity than they were prior to initiating treatment.
8) Based on our experience gained in this maintenance study, we suggest the following guidelines to prevent or treat such symptoms: a) Decrease daily dosage by 2.5 to 5 mg but not more than one-fourth the daily dose every 1-2 weeks. b) Patients with transient reactions, short-lasting symptoms, or patients who do not mind suffering through their withdrawal reactions, may not need any treatment at all, at least when diazepam, a drug with a long half-life, is involved. Convulsions or psychotic reactions were not observed in our study. c) Original symptoms may frequently return. They are never as abrupt, distressing, and different from original symptoms than withdrawal reactions.
9) Finally, 96 patients who completed the maintenance phase were followed by mail interview 12 months after completion of the study. Table 3 gives results from the 1-year followup. These results are most disturbing. Of the 96 patients for whom data are available, 59% were symptomatic at time of followup, this despite the fact that all patients were asymptomatic while on diazepam; and of the 57 symptomatic patients, less than 50% were treated for their symptoms. This treatment involved not only benzodiazepines, but also tricyclic antidepressants (TCA) and neuroleptics. Interestingly, none of these 27 patients had entered psychotherapy or other nondrug treatments. While the use of TCAs is probably appropriate since patients may have become depressed, the use of neuroleptics in seven patients subjects these patients to potentially more dangerous drugs than the benzodiazepines.
10) In summary, more than 50% of chronically anxious patients need at the most only 6

weeks of treatment with diazepam to remain symptom free. Those patients who need continued maintenance treatment do not develop tolerance to their medication, but also do not continue to improve beyond the improvement levels they had reached after 6 weeks of treatment. A return of symptoms is usually indicated by a slow onset and a recurrence of symptoms which are similar to the ones originally present. Withdrawal reactions due to abrupt discontinuation of diazepam range from mild and transient to more severe and very disturbing. They show a rather acute onset, with symptom intensity peaking after 5 to 7 days and with symptoms being much more disturbing than the original symptoms present prior to treatment. These symptoms include many symptoms not present originally. Withdrawal reactions can be prevented in most patients by stepwise reduction of dosage.

Table 3

One-Year Followup
***N* = 96**

	Symptoms Present	Symptoms Absent
Treatment	57 (59 %)	39
Yes	27*	1 (Hypnosis by GP)
No	30	0

*Type of Treatment:

Benzodiazepines (Valium: 12 Other: 4)	16
Neuroleptics	7
TCA	4

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Behavioral Assessment of Drug Effects In Obsessive-Compulsive Disorders

Samuel M. Turner, Ph.D.[1]

Research can only advance as far as is permited by our measurement technology. Yet, it is a truism in clinical research that the technology of measurement lags significantly behind research endeavors. The quantity of research appears to exceed what can be justified from the standpoint of measurement quality. Clinical research typically grows out of the existence of interesting and significant clinical problems, and the need to develop some information about pathological behavior in the clinical arena. Thus, there is often little primary attention given to the perplexities of measurement issues.

Clinical studies are often designed to compare treatments with one another, placebo, or no treatment. A typical set of measurements consists of one or more of the following: patient self-report, clinical ratings, and paper and pencil inventories. It is not that there is anything wrong with applying these measures; rather, it is a question of whether or not this represents a completely adequate measurement strategy for the phenomena under consideration. The proper measurement system is essential if treatments (or no treatment) are to be adequately evaluated. A measurement strategy must be developed for a given disorder according to the phenomena under study as well as logical, theoretical, and practical considerations.

In recent years, there has been increased optimism in our thinking concerning the treatment of obsessive-compulsive disorder. Throughout the history of psychiatry, this disorder has been noted for its resistance to most forms of treatment (Grimshaw, 1965; Kringlen, 1965). However, recent studies with pharmacological (Thorén, Åsberg, Cronholm, Jörnestedt, & Träskman, 1980; Thorén, Åsberg, Bertilsson, Mellstrom, Sjöquist, & Träskman, 1980), surgical (Bridges, Goktepe, & Martos, 1973; Mitchell-Heggs, Kel-

[1]Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, PA 15261.

Reprint requests to Samuel M. Turner, Ph.D., Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15261.

ly, & Richardson, 1976) and behavioral interventions (Rachman, Cobb, Grey, MacDonald, Mawson, Sartori, & Stern, 1979; Turner, Hersen, Bellack, Andrasik, & Capparell, 1980; Turner, Hersen, Bellack, & Wells, 1979) have produced encouraging results with relatively brief periods of treatment. In most instances, psychosurgery would not be considered an appropriate treatment in this country. Therefore, drug treatment and behavior therapy appear to be the treatments of choice.

Obsessive-compulsive disorder is characterized by recurrent or persistent ideas, images, thoughts, or impulses. These are typically accompanied by an urge to engage in some overt or covert act, usually of a repetitous nature. Along with these subjective symptoms are the well-known behavioral abnormalities which include rituals such as hand washing, checking, and various avoidance behaviors. Rituals often significantly interfere with normal daily functions such as bathing, eating, toileting, and grooming. Moreover, social, economic, vocational, and interpersonal disfunctions may be experienced. In addition, varying degrees of depression and anxiety are an integral part of the syndrome.

Given the complex behavioral and physiological (biochemical) dimensions of the disorder, it is essential that a multifaceted measurement system be employed in research studies. This is rendered even more important if one desires to study the poorly understood relationship of depression and anxiety to obsessive-compulsive disorder. Presently, even the best studies of drugs (e.g., Rachman et al., 1979; Thoren et al., 1980 a,b) employed a set of incomplete outcome measures. Any measurement strategy should involve assessment of self-report, overt behavior, and physiological changes. That results may vary dependent upon the channel of measurement employed is a well-know phenomena. For example, following behavioral treatment, phobics may be able to approach formerly fear-inducing stimuli but still indicate by self-report that they are fearful, while changes in physiological indicators are consistent with their new behavior. This discrepancy among channels of measurement has been labeled desynchrony by Rachman and Hodgson (1974).

Keeping the tripartite measurement system described above in mind, listed below are the elements of an adequate measurement system for employment in obsessive-compulsive research. First, there should be some type of self-report measurement of obsessive ideation. This should consist of paper and pencil inventories, interview ratings, daily self-monitoring, or some combination. Specific measurement of overt ritualistic behavior is best obtained through direct behavioral observations as illustrated by the Turner et al. (1979, 1980) studies. Unfortunately, such direct observations are not always practical. Therefore, some form of self-report or interview ratings might also be necessary.

When direct observational data cannot be obtained, one way to remedy the stituation is to employ a behavioral avoidance test similar to those used in phobic research. Anxiety should be measured in all three measurement channels. Self-report data can be obtained via daily ratings of tension, interview ratings, or paper and pencil inventories. Behavioral data can be obtained by direct observation of operationally defined anxiety behaviors (e.g., fidgeting or hand-wringing). Physiological processes are probably more appropriate in anxiety measurement than in any of the other aspects of obsessive-compulsive disorder. Such measures as heart rate and galvanic skin response (GSR) would be appropriate. However, in the obsessive-compulsive syndrome, another set of physiological measures is necessary if we are to understand the mechanism by which drug effects are obtained. These are biochemical measures such as the ones employed in the Thoren (1980) and Rachman et al. (1979) studies. Depression can be measured by a number of self-report scales. It can also be measured by interview ratings, and through direct behavioral observation. Finally, some type of measurement of social functioning should be employed to assess all relevant social role areas. Such social functioning data should be obtained from the patient himself as well as from significant others. An outline of the use of the tripartite measurement system in obsessive-compulsive disorder is presented in Table 1.

Prior studies in obsessive-compulsive disorder had typically grouped all of the obsessional states together and treated them with drugs or some other form of treatment. Yet, it appears from the clinical literature that subgroups of obsessive-compulsive patients might exist. If there are in

Table 1

Assessment Strategy for Obsessive-Compulsive Disorder*

	Obsessive-Compulsive Symptoms				
	Subjective Distress	Rituals/Avoidance Behavior	Anxiety	Depression	Social / Interpersonal Functioning
Self-Report	X	X	X	X	X
Behavioral		X	X	X	
Physiological**			X	X	

*The channel of measurement that can be employed will vary to some extent with the nature of the problem.

**Physiological measures include biochemical assays.

fact important differences among types of obsessives, it is essential to begin developing classification systems so that the effects of treatments can be clearly defined. For example, Mavissakalian (1980) proposed a "functional" classification of obsessive-compulsive phenomena (*see* Table 2). Although the clinical and theoretical value of this system has not been established, it is a beginning in an area that has lacked serious investigation.

Considerable evidence has accumulated to suggest that antidepressants such as clomipramine are an effective treatment agent for obsessive-compulsive disorder. Moreover, there is recent evidence to suggest that a specific dose range is more effective than others, and that the proposed mechanism of change is suppression or the reuptake of serotonin. Yet, it was suggested above that the measurement strategies employed in previous studies were not wholly adequate. Therefore, it is difficult to assess the value of drug treatments at this time. Finally, a word of caution is also in order concerning the sample size used in experimental studies. Given the number of measures needed to adequately assess the obsessive-compulsive syndrome (*see* Table 1), it is evident that multivariate procedures may be required, or at least adjustment of significance levels. Moreover, in order to obtain adequate statistical power (cf. Agras & Jacob, 1981) when comparisons of active treatments are made, sample sizes far in excess of what typically is employed will be required. The presence of obsessive-compulsive disorder is consistently estimated to be low in comparison to other anxiety disorders. Therefore, in order to conduct a study with with the proper sample size, multicenter studies might be necessary.

Table 2

Functional Classification of Obsessive-Compulsive Phenomena

Obsessions—noxious cognitive stimuli such as intrusive thoughts, images, feelings and impulses

Obsessions Plus Compulsions (Anxiety Reducing)—behaviors which attempt to neutralize obsessions and reduce anxiety, discomfort (washing, checking, other cognitions, etc.)

Obsessions Plus Obsessionalized Compulsions (anxiety augmenting)—development of obsessional secondary phenomena

Rituals (Autonomous Compulsions)—rituals are disassociated from the anxiety/discomfort producing obsessions

From Mavissakalian (1980), *Journal of Behavioral Assessment*. Reprinted by permission.

Clinical Trials of Neuropeptides in Psychiatric Disorders

Chair: **Philip A. Berger, M.D.**
Department of Psychiatry and Behavioral Sciences
Stanford University Medical School
Stamford, California

and

Jerome Levine, M.D.
Pharmacologic and Somatic Treatments Research Branch
National Institute of Mental Health
Rockville, Maryland

Effect of Des-Tyr-γ-Endorphin in Schizophrenia
Herbert Meltzer, Daniel A. Busch, John Lee, and Yiannis Papaçostas
University of Chicago, Chicago, IL and SUNY at Stony Brook, NY

*Des-Tyr-γ-Endorphin: Clinical Experience in Depression
Thomas Meehan, Lynn Johnson, Yiannis Papacostas, and Max Fink
SUNY at Stony Brook, Stony Brook, NY

Vasopressin Studies in Alzheimer's Disease
Carol Tamminga, Raymon Durso, Paul Fedio, and Thomas N. Chase
Maryland Psychiatric Research Center and University of Maryland School of Medicine and National Institutes of Health

*Denotes paper was presented at NCDEU meeting but not received before going to press.

Effect of Des-Tyr-γ-Endorphin in Schizophrenia

Herbert Y. Meltzer, M.D.,[1] Daniel A. Busch, M.D.,[2] John Lee, M.D.,[3] and Yiannis Papacostas, M.D.[3]

Des-tyr-gamma-endorphin (DTγE) is a peptide which may occur endogenously, (Verhoef, Loever, Burbach, et al., 1980), and which has been shown in animal studies to have some behavioral, biochemical, and electrophysiological effects which are comparable to those of classical neuroleptics (de Wied, Bohus, van Ree, et al., 1978; Nickolson, & Berendsen, 1980; Pedigo, Schallert, Overstreet, et al., 1979; Schoemaker, & Nickolson, 1980). There are also significant differences between DTγE and neuroleptics, such as inability to produce catalepsy or block apomorphine-induced stereotypy (de Wied, Kovacs, Bohus, et al, 1978; Weinberger, Arnsten, & Segal, 1979). This profile has led to a series of clinical trials designed to determine if DTγE has antipsychotic properties in man. As with many antipsychotic compounds, early results were very favorable, indicating that doses as low as 1 mg/day intramuscularly (i.m.) for as brief a period as 3 days produced considerable improvement in both chronic and acute schizophrenic patients, although the results were far from uniform

[1]University of Chicago School of Medicine and Illinois State Psychiatric Institute, Chicago, IL 60637.
[2]Illinois State Psychiatric Institute, Chicago, IL 60637.
[3]State University of New York, Stony Brook, NY 11794.

(Emrich, Zandry, Zerssen, et al., 1980; van Ree, de Wied, Verhoeven, & van Praag, 1980; Verhoeven, van Praag, Botter, et al., 1978; Verhoeven, van Praag, van Ree, & de Wied, 1979). No extrapyramidal side effects were noted. More recently, entirely negative results have been reported in schizophrenic patients with and without tardive dyskinesia (Casey, Korsgaard, Gerlach, et al., 1981; Tamminga, Tighe, Chase, et al., 1981).

Method

This study included two groups of subjects. The first consisted of eight newly hospitalized schizophrenic patients at the Illinois State Psychiatric Institute who were diagnosed schizophrenic according to Research Diagnostic Criteria (Spitzer, Endicott, & Robins, 1977). Six were chronic, one subacute, and one acute. There were five males and three females; the mean age was 24.8 years. Following admission, the patients were kept off active medication for a period of 9 to 25 days. There was no appreciable symptom change during this time. Treatment with DTγE was begun with an initial dose of 1 mg i.m. daily for at least 3 days. The dose was randomly adjusted on an open basis to 3-10 mg/day for the rest of the 12-day treatment period. The maximum dose was 3 mg/day in four patients, 5 mg/day in two patients, and 10 mg/day in two patients. Following treatment with DTγE, patients were not given active medication for at least a week. Clinical change was assessed with the Schedule for Affective Disorders and Schizophrenia (SADS) (Spitzer & Endicott, 1980), the Global Adjustment Scale (GAS) (Endicott, Spitzer, Fleiss, & Schen, 1976), and the Nurses' Observation Scale for Inpatient Observation (NOSIE) (Honigfeld, Gillis, & Klett, 1966).

The Hoffman-reflex (H-reflex) recovery curve (Metz, Busch, & Meltzer, 1981) and platelet monoamine oxidase (MAO) activity (Jackman & Meltzer, 1980) were determined at the end of the placebo period as well as during and after the post-DTγE treatment period. Serum prolactin levels were determined by radioimmunoassay.

The second group of subjects consisted of seven patients hospitalized at the Veterans Administration Hospital or University Hospital at Stony Brook. Seven schizophrenic patients were treated with DTγE in doses of 1-4 mg/day for 14-21 days. Clinical evaluation was by means of the Brief Psychiatric Rating Scale (Overall & Gorham, 1962) and the Clinical Global Scale.

Results

The overall clinical impression of the research staff was that two of the eight Chicago patients showed marked clinical improvement, four showed minimal to moderate improvement, and two showed no change. Changes in GAS scores were in the direction of improvement in seven of eight patients (*see* Figure). These improvements were slight, but of the order of magnitude noted in other schizophrenic patients in the author's research unit who have been treated with classical neuroleptic treatment for a comparable period. Improvement was mainly in the area of social functioning. Patients became less withdrawn and more sociable and cooperative. Reports of delusions and hallucinations decreased in the responses given during SADS interviews, but clinical staff did not believe meaningful improvement occurred in these areas. Improvement in social functioning began within the first 3-7 days of treatment and did not appear to be dose-related. No extrapyramidal or other side effects were noted. After discontinuation of DTγE, six of eight patients showed deterioration. Considerably greater improvement was noted in these patients during the neuroleptic treatment period which followed DTγE. One of the two apparent good responders to DTγE failed to show any improvement on DTγE when treated with a subsequent course of DTγE upon rehospitalization 6 months later.

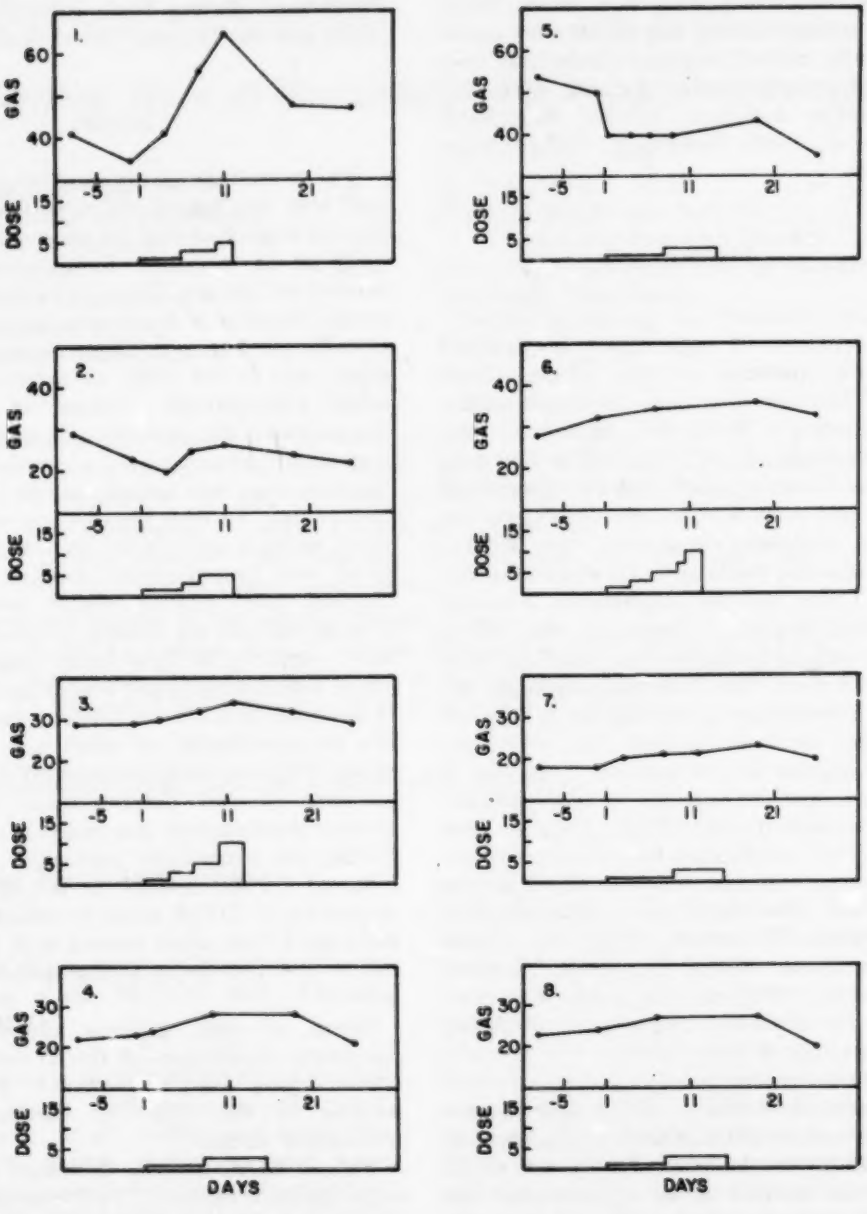
Seven of eight patients showed decreased secondary facilitation of the H-reflex recovery curve during DTγE treatment. This is comparable to the effect of clinically effective neuroleptic drugs.

Platelet MAO activity decreased in six of the eight patients during DTγE treatment. This is also comparable to the effect of neuroleptic drugs.

No change in serum prolactin levels was observed for up to 4 hours after injection of 1 mg DTγE.

Of the seven Stony Brook patients, one chronic

GLOBAL ASSESSMENT SCALE BEFORE, DURING AND AFTER DTGommaE



schizophrenic patient who had failed to respond to neuroleptic treatment showed marked, persistent clinical improvement of both positive and negative symptoms, and two showed moderate but transient improvement. No effect of DTγE on serum prolactin levels was noted.

Discussion

The clinical change during the period of treatment with DTγE was not impressive on an overall basis. An open study such as this has significant biases toward a type II error because of the high expectations of patients and staff of a novel antipsychotic agent. The major clinical improvement was noted in areas of behavior which are least objective to assess and most sensitive to high expectations for some improvement. The failure to obtain improvement in positive symptoms comparable to that produced by neuroleptic treatment is suggestive that DTγE is less effective than classical neuroleptic drugs if indeed it is active at all.

We did find two biological measures of activity of DTγE: the H-reflex and platelet MAO. The effects on these parameters were those produced by classical neuroleptic drugs. This is encouraging in that there may indeed be an in vivo neuroleptic effect of DTγE.

A double-blind, placebo-controlled study of DTγE for longer periods of time in a larger sample seems indicated, despite the meager clinical improvement demonstrated here because of the evidence of biological effects of DTγE. It may be that only a small proportion of subjects would respond clinically to this peptide because of heterogeneity of schizophrenia or because of differences in absorption and metabolism of DTγE.

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Vasopressin Studies in Alzheimer's Disease

Carol A. Tamminga, M.D.,[1] Raymon Durso, M.D.[1] Paul Fedio, Ph.D.[1] and Thomas N. Chase, M.D.[1]

Recent advances in peptide pharmacology are suggesting areas for therapeutic application of exogenous peptides in human disease. Vasopressin, identified since 1950 as a cyclic-nine amino-acid peptide involved in sodium excretion and smooth muscle contraction, has been shown to facilitate animal learning and memory in behavioral testing. Peripherally administered vasopressin delays extinction of learned behaviors in a variety of animal learning paradigms (Ader & de Wied, 1972; Bohus, Gispen, & de Wied, 1973; de Wied, 1971; de Wied, Greven, Lande, & Witter, 1972). Furthermore, Brattleboro rats, which on a genetic basis lack vasopressin, learn behaviors more slowly and extinguish learned behaviors faster than control rats; this defect is corrected by the exogenous administration of vasopressin (de Wied, Bohus, & Wimersma, 1975). Moreover, analogues of vasopressin have been shown to block the effects of CO_2-induced retrograde amnesia in rats tested in a passive avoidance task (Rigter, Riezen, & de Wied, 1974). Recent uncontrolled trials of vasopressin in human memory-losing disorders (Weingartner, Gold, Ballenger, et al. 1981; Oliveros, Jandali, Timsit-Berthier, et al. 1978; LeBoeuf, Lodge, & Eames, 1978; Blake, Dodd, & Evans, 1978) as well as in normal individuals (Weingartner et al., 1981; Legros, Gilot, Seron, et al. 1978) have encouraged further controlled testing.

Method

Lysine vasopressin was administered in a double-blind, placebo-controlled design to patients with mild to moderate symptoms of Alzheimer's-type dementia. Patients were included if they had a progressive history of memory loss and cognitive deficit, documented by the Wechsler Adult Intelligence Scale (WAIS) and the Wechsler Memory Scale (WMS), without any evidence of focal brain impairment or other diagnosable cause of dementia. The study design was a non-crossover type using seven patients in each of two groups, one of which received 16 units per day of vasopressin administered intranasally, the other, an equivalent quantity of nasal spray carrier for 10 days. Subjects were evaluated with memory and performance tests prior to, during, and for 7 days following the intranasal treatment. The tests administered were selected to measure aspects of learning, memory, attention, and perception in each of the patient participants. At baseline, the WAIS and the WMS were done to confirm the diagnosis of Alzheimer's disease, and the initial battery of learning tests was applied. The specific learning and memory tests carried out were: 1) word list learning with free recall and selective reminding; 2) paired associate learning for immediate and delayed recall; 3) memory retention for a 20-item paragraph-long prose passage in immediate and delayed recall; 4) memory retention for photographs of common objects; 5) reaction time using a standard key-press machine with either fixed or variable forewarning period; and 6) perception capacity with a tachistoscope projecting patterns and words to the central visual field.

Results and Discussion

Results showed no difference in learning or memory between lysine vasopressin (LVP)-treated and placebo-treated subjects. Immediate recall and learning were unchanged in word list and paired associate learning and in the memory retention tests. Delayed recall testing, included to measure aspects of memory storage and recall, also remained unchanged. However, the tests of fixed alerting-interval reaction time showed that the subjects who received vasopressin reacted faster than those who received placebo. When a variable alerting-interval was used, no difference in reaction time was apparent between the vasopressin and placebo-treated groups.

We report that lysine vasopressin failed to enhance memory or learning in human subjects with Alzheimer's disease, while it did improve reaction time. The fixed-interval reaction time test in-

[1]National Institute of Neurologic and Communicative Disorders and Stroke, Bethesda, MD 20205, and Maryland Psychiatric Research Center, Baltimore, MD 21228.

dicates either an enhancement of motor response or attention or both. Our results suggest a nonspecific activating effect of vasopressin. This effect, similar to that expected with other central nervous system stimulants, like amphetamine, may well enhance learning and/or memory in noncognitively impaired individuals. The basal organic impairment of this patient group may account for their failure to respond to vasopressin.

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Psychoactive Drug Treatment In Retarded Populations

Chair: **Robert L. Sprague, Ph.D.**
Institute for Child Behavior and Development
University of Illinois
Champaign, Illinois

and

Robert Lipman, Ph.D.
Pharmacologic and Somatic Treatments Research Branch
National Institute of Mental Health
Rockville, Maryland

Effects of Phenytoin Withdrawal on Matching to Sample and Workshop Performance of Mentally Retarded Individuals—A Brief Report
Vicky J. Davis
Western Psychiatric Institute and Clinic, Pittsburgh, PA

Effects of Neuroleptic Drugs on the Intellectual and Habilitative Behaviors of Mentally Retarded Persons
Donald G. Ferguson
Mental Retardation Division, Brainerd State Hospital, Brainerd, MN

An Applied Dose-Response Curve of Thioridazine with the Mentally Retarded: Aggressive, Self-stimulatory, Intellectual, and Workshop Behaviors—A Preliminary Report
Stephen E. Breuning
Western Psychiatric Institute and Clinic, Pittsburgh, PA

An Analysis of Institutionalized Retarded Residents Using DIS-CO
Robert L. Sprague
Institute for Child Behavior and Development, University of Illinois, Champaign, IL

Tardive Dyskinesia in Mentally Retarded Children, Adolescents, and Young Adults: North Carolina and Michigan Studies
C. Thomas Gualtieri, Stephen E. Breuning, Steven R. Schroeder, and Dana Quade
University of North Carolina, Chapel Hill, NC and Western Psychiatric Institute and Clinic, Pittsburgh, PA

Comment on Neuroleptic Serum Levels in Mentally Retarded Boys
James C. Harris, Larry E. Tune, Michael Kurtz, and Joseph T. Coyle
Johns Hopkins University School of Medicine, Baltimore, MD and University of Pennsylvania School of Medicine, Philadelphia, PA

Effects of Phenytoin Withdrawal on Matching to Sample and Workshop Performance of Mentally Retarded Individuals—A Brief Report[1]

Vicky J. Davis, M.A.[2]

Phenytoin is used with about 40% of institutionalized and non-institutionalized mentally retarded individuals and has been the medication of choice for the control of seizures with all types of populations. Despite its widespread use, only recently have studies begun to examine the effects of phenytoin on measures of learning, performance, and adaptive behavior with the mentally retarded. The present investigation was designed to examine the behavioral effects of phenytoin withdrawal on two procedural tasks with institutionalized mentally retarded individuals: a matching to sample (MTS) color discrimination task and a workshop bicycle brake assembly (Bendix RB-2) task.

The subjects were two female (D & L) and one male (E) institutionalized mentally retarded individuals who had each been receiving phenytoin for at least three consecutive years. Criteria for phenytoin withdrawal was the absence of observed seizures during this 3-year period. None of the subjects were receiving any other antiepileptic or neuroleptic medications. Subjects D, L, and E were 27, 23, and 16 years old, respectively. Subject D was receiving 100 mg oral dose of phenytoin, while Subjects L and E were each receiving 300 mg (100 t.i.d.) oral doses at the beginning of the study. Baseline phenytoin/serum levels for D, L, and E were 3.0 μg/ml, 4.1 μg/ml, and 3.5 μg/ml, respectively.

Method

Matching to Sample

The zero delay matching to sample (MTS) procedure involved a simple discrimination procedure using color stimuli. Each subject was seated in front of the intelligence panel where the center response window was illuminated with one of three colors (sample stimulus). Pressing the center window terminated its illumination and simultaneously resulted in the illumination of the two side windows (comparison stimuli). One of the side windows was illuminated with the same color (matching stimulus) as the center window (sample stimulus) and the other was illuminated with a different color (non-matching stimulus). Randomization of color assignments for each window occurred, with each color appearing equally often as sample, matching, and non-matching stimuli.

A matching response resulted in the delivery of one consumable reinforcer, and an 0.5 sec, 1000 hz tone. A non-matching response or no response within 30 sec terminated the side window illuminations for a 10-sec timeout prior to the onset of the next trial (i.e., illumination of the center window). The failure to emit a response within 30 sec was counted as an error. Five sec after reinforcement delivery or 10 sec after an incorrect reponse (error), the center window was illuminated to begin the next trial. Each incorrect response resulted in the stimulus being repeated until a correct response was emitted. The dependent variable was the percentage of correct responses per session. Each subject participated in two or three sessions per week with each session consisting of 30 trials. The first three sessions were pretraining sessions where the matching-to-sample procedure was followed and the subjects were given vocal and physical prompts that were gradually faded out until the subjects were able to respond independently. The fourth session began the experiment proper, in which phenytoin doses were systematically reduced following a multiple-baseline-across-subjects design (Baer, Wolf, & Risley, 1968). Subject D received one dose reduction (100 mg to 0 mg) while Subjects L and E received two reductions (300 mg to 150 mg to 0 mg). The number of daily phenytoin administrations remained consistent as dose reductions oc-

[1]This study was partially supported by USPHS Grant MH-32206 from the National Institute of Mental Health. A complete version of this paper appears in the *Journal of Nervous and Mental Disease* (Davis, V.J., Poling, A.D., Wysocki, T., and Breuning, S.E. Effects of phenytoin withdrawal on matching to sample and workshop performance of mentally retarded persons 169(11): 718-729, 1981).

[2]Substance Abuse Clinic, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, PA 15261.

curred, and an inactive placebo was administered once 0 mg was reached.

Workshop

A retrospective analysis of Subjects D and L's performance on a workshop assembly task was performed once the matching to sample sessions were completed. The workshop task involved the assembly of a 15-part coaster bicycle brake assembly (Bendix RB-2) (Gold, 1972, 1973). Each brake was assembled individually by each subject utilizing a 15-compartment tray for sequential assembly. The three response measures recorded were percentage of time on task, number of assemblies completed, and number and type of prompts required from teacher or aides. Interobserver agreement checks by the workshop supervisor were completed on 15% of the teachers' and aides' ratings. The mean percentage of agreement was 89.6% with a range of 79.4% to 98.6% across sessions.

Serum Levels—EEG Assesments

Both phenytoin serum levels (gas liquid chromatography) and electroencephalogram (EEG) assessments were completed prior to baseline (within 5 days of Session 1) and the final reduction (10 to 14 days after matching to sample Sessions 13, 42, and 55 for Subjects D, L, and E; and workshop Sessions 19 and 54 for Subjects D and L, respectively). An additional phenytoin/serum level EEG was completed 4 days after the onset of the 150 mg dose for Subjects L and E (MTS Sessions 22 and 30, respectively, for L and E, and workshop Session 33 for L). Seizure monitoring procedures were in effect throughout the study. Double-blind procedures were implemented throughout; neither ward staff, workshop staff, nor subjects were aware of the phenytoin dose reductions or placebo administrations.

Results

The results of the study empirically demonstrate that doses of phenytoin considerably lower than the suggested optimum therapeutic level of 10-20 μg/ml (Rall & Schleifer, 1980) can impair the performance of mentally retarded individuals on both matching to sample and work assembly tasks. As the doses were reduced for each of the three subjects, there were increases in matching to sample task, with the highest percentage correct being obtained after, and only after, the 0 mg dose was reached. The greatest number of brake assemblies completed and lowest numbers brake assemblies completed and lowest numbers of prompts required in the workshop setting occurred only after the 0 mg dose was reached. There was no substantial change in the percentage of time-on-task for either subject in the workshop setting. Also, there were no EEG changes across withdrawal, and the results correlated with serum level changes.

Conclusion

The findings from this study have serious implications for the mentally retarded who receive phenytoin. While the subjects in the study are perhaps not typical of most epileptics receiving phenytoin, there are a great number of mentally retarded individuals receiving phenytoin of whom they are representative. It is not unreasonable to generalize the present findings to other mentally retarded individuals who are receiving phenytoin and have been seizure free for extended periods of time. For example, recent estimates suggest that about 28% of all the mentally retarded receiving phenytoin have not had observed seizures (Davis, Cullari, & Breuning, in press). This suggests that large numbers of the mentally retarded are experiencing an unnecessary drug-induced impairment in performance. However, it is important to mention that even though none of the subjects showed evidence of a clinical seizure while receiving phenytoin or following withdrawal, this certainly does not indicate that all mentally retarded individuals receiving phenytoin, but remaining seizure free for an extended period of time could be successfully titrated off of the drug. Probably some could not. However, given the possibility of behavior and impairment, conservative use of phenytoin is warranted.

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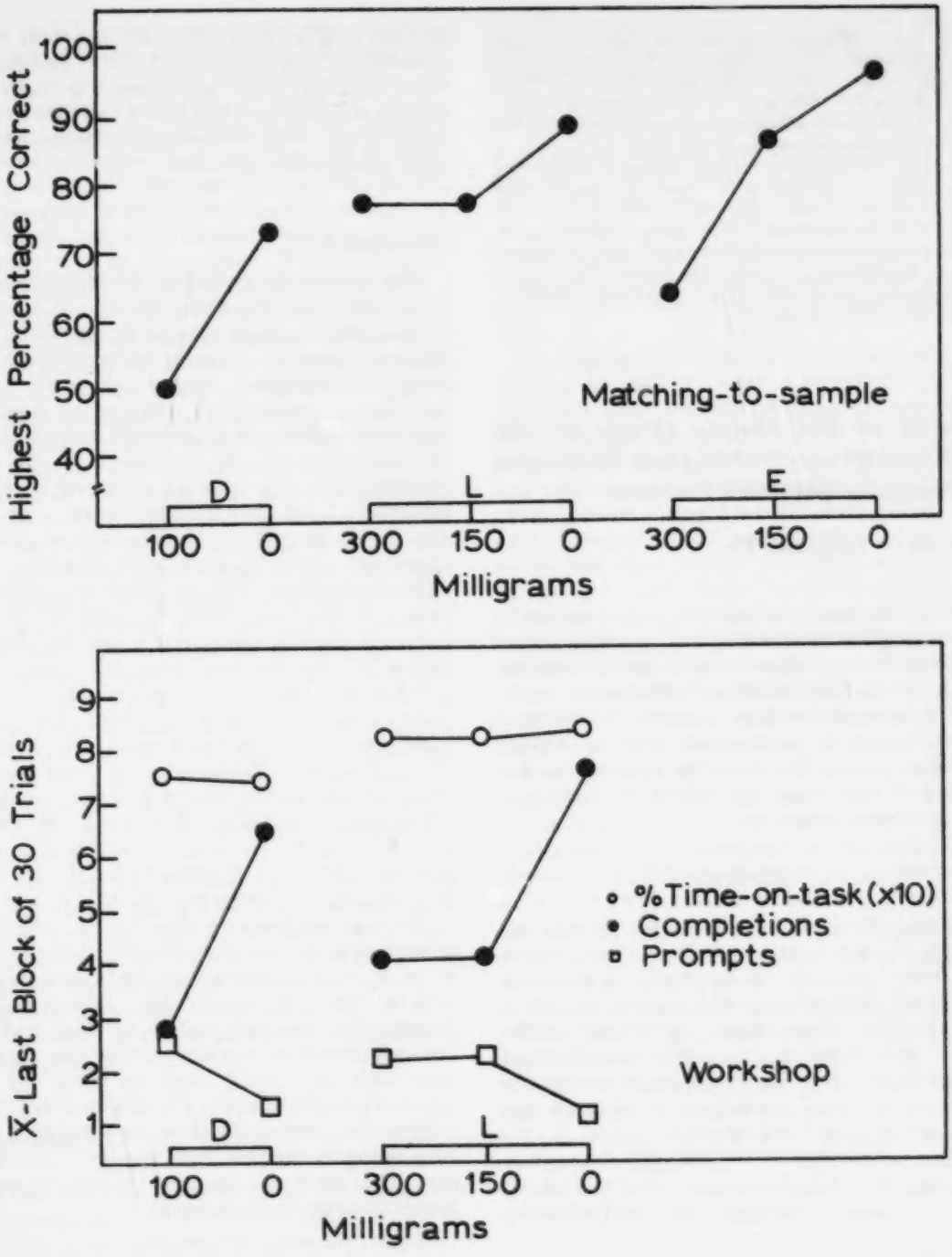

FIGURE. The Figure summarises the matching to sample and workshop performance of Subjects D, L, E and D, and L, respectively.

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Effects of Neuroleptic Drugs on the Intellectual and Habilitative Behaviors of Mentally Retarded Persons[1]

Donald G. Ferguson, Ph.D.[2]

There has been a paucity of studies examining behavioral alternatives to neuroleptic drug control of inappropriate behaviors with institutionalized mentally retarded persons. Furthermore, only a few of these studies have assessed the effects of these drugs on IQ scores or performance in habilitative programs. The following studies were conducted to determine the effects of neuroleptic drugs in these areas.

Method

A total of 162 mentally retarded persons participated in four studies (i.e., Breuning & Davidson, 1981; Breuning, Davis, Matson, & Ferguson, under review; Breuning, Ferguson, Davidson, & Poling under review; Breuning, O'Neill, & Ferguson, 1980). The 79 males and 83 females ranged in age from 11-71, had IQs between 19 and 64, and were receiving one neuroleptic drug for time periods ranging from 0.1-3.7 years. In Experiments 1 and 2, participants were on thioridazine, chlorpromazine (CPZ), mesoridazine, lithium carbonate, or haloperidol in dosages ranging from 200-1,500 mg daily (CPZ equivalent). In Experiments 3 and 4, participants were receiving only thioridazine in daily mg dosages ranging from 100-800. In all four studies, when drugs were withdrawn, placebo/double-blind procedures were used.

Experiment 1

This experiment compared the effectiveness of neuroleptic drug (D), response-cost (RC), and D + RC procedures for controlling aggressive and psychotic behaviors. Prior to the beginning of this study, all participants received tokens for engaging in a variety of appropriate/adaptive behaviors. When the experiment proper began, the token economy did not include an RC contingency (loss of tokens for engaging in target behaviors). All participants were receiving neuroleptic drugs for behaviors such as physical aggression, property destruction/disruption, and yelling/screaming. The two treatment sequences were: D (base-line), D + RC, and RC for Sequence 1 and D, placebo (P), and RC for Sequence 2. In the first sequence, drugs were withdrawn during the first 3 weeks of the RC condition. In the second sequence they were withdrawn during the first 3 weeks of the P condition. The mean frequencies of inappropriate behaviors during the last week of each condition of Sequence 1 were 50.2, 49.6, and 5.2 for the D, D + RC, and RC conditions, respectively. In Sequence 2, the mean frequencies for the D, D + RC, and RC conditions were 46.3, 51.3, and 3.7.

It is apparent from the data that the behavioral procedure alone was more effective than the drug alone or in combination with the behavioral procedure. Also, the results from Sequence 2 illustrate that the combination of drug and behavioral procedure was not necessary as a transition stage from drug alone to using the behavioral procedure alone. The results of this study suggest that neuroleptic drugs can interfere with responding to external reinforcement contingencies. This issue was examined further in a different situation in Experiment 2.

Experiment 2

In this experiment, the effect of neuroleptic

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[2]Developmental Disabilities Program Division, Brainerd State Hospital, Box 349, Brainerd, MN 56401.

drugs on IQ scores was assessed when residents were tested under standard (i.e., following procedures in test manual) and reinforcement (an edible reinforcement given for each correct response) conditions. IQ tests were administered on three occasions, each separated by 60 days. The participants were divided into four groups and assigned to one of four condition sequences. During the first two test administrations all participants were receiving drugs. Test 1 was given under standard conditions for all groups. Test 2 was given under standard conditions for Groups 1 and 3 and reinforcement conditions for Groups 2 and 4. During the third test, the groups were tested under the same conditions as Test 2. However, Groups 1 and 2 were taken off medication during the first 3 weeks following the second test. Groups 3 and 4 remained on drug.

While all four groups were on drugs there were no differences in IQ scores, regardless of whether tests were administered under standard or reinforcement conditions. The mean IQ scores for the four groups on the first and second test were 24.8, 27.6, 24.2, 26.3 and 25.7, 24.5, 24.0, and 26.9, respectively. On the third test the mean IQ scores for the four groups were 32.6, 54.7, 24.2, and 25.4, respectively. The two groups tested off drug showed mean increases of 6.9 IQ points (standard conditions) and 30.2 IQ points (reinforcement conditions). But the other two groups tested on drugs showed only slight changes. The results of this study support and extend the findings of Experiment 1.

In the first two studies, all participants had been previously selected for drug discontinuation because they displayed a high frequency of inappropriate behavior while on drug. Therefore it could be argued that the results are specific to those individuals who do not respond to neuroleptic drug treatment. This possibility was examined in a third study.

Experiment 3

There were two equal divisions (20 responders and 20 nonresponders) of participants formed on the basis of data gathered in a prestudy drug trial. The 20 responders were individuals showing decreased frequencies of inappropriate behaviors (at least 60%) while on thioridazine and 20 nonresponders were individuals showing no change (less than 10%) or increased frequencies of inappropriate behaviors while on drug. The prestudy drug trial used an ABA design (on-drug, off-drug, on-drug). Both the responders and nonresponders were each divided into four groups and exposed to the same condition sequences as described for Experiment 2. However, the time periods between test administrations were not equal. Tests 1 and 2 were separated by 8 weeks and Tests 2 and 3 were separated by 12 weeks. Drugs were titrated over a 3-week period from Week 10 to Week 13 of the study.

The frequency of inappropriate behaviors (e.g., physical aggression) were recorded throughout the study. There was little difference in scores for any of the groups on the first two tests. On the third test, Groups 1 and 2 of both the responders and nonresponders had been off drugs for 9 weeks while Groups 3 and 4 remained on drugs. For both responders and nonresponders, the only substantial score changes on Test 3 occurred in the groups tested under the off-drug/reinforcement condition. The mean increase in IQ score for these groups was 26.5 and 24.4 IQ points for responders and nonresponders, respectively. Mean test score changes for all other groups ranged from -2.9 to $+4.1$ points. There was little change in the frequency of inappropriate behaviors while all the groups were receiving thioridazine. However, when the drug was withdrawn from the two groups in each division of responders and nonresponders, the responders showed a significant increase in inappropriate behaviors, and the nonresponders frequencies significantly decreased. There is one disparate finding between Experiment 2 and 3. In the former study, increases in test scores were found under both standard and reinforcement conditions when drugs were withdrawn, while in Experiment 3 significant increases were found only under reinforcement conditions off-drug. The basis for this discrepancy is unclear. However, it is apparent that in both studies reinforcement procedures in the absence of neuroleptic drugs resulted in large increases in IQ scores for both responders and nonresponders.

Experiment 4

The final experiment was designed to assess the

effect of thioridazine on the performance of a workshop task (assembly of a 15-part bicycle coaster brake). In addition, the effect of gradual vs. abrupt drug withdrawal and drug initiation was assessed. The study was conducted over a 29-week period. The conditions were abbreviated as follows: D-drug; ND-no drug; A-abrupt; withdrawal (end of Week 10); G-drug discontinued gradually over a 3-week period (Weeks 20-22). The groups were designated D-D, D-NDA, D-NDG, ND-D, and ND-ND where the letters before the hyphen refer to the first 10 weeks of the study and the letters after the hyphen refer to Weeks 11-29. Although three response measures were taken (time-on-task, number of prompts, and number of completions), the clearest drug effects were observed on the last measure and only they will be discussed.

Analyses showed that by the tenth week the two groups not receiving drugs (ND-D and ND-ND) were completing more assemblies than the others. On Weeks 12-15 the two groups not receiving drug (ND-ND, D-NDA performed significantly different than the other groups. Group ND-ND continued to improve while group D-NDA's performance deteriorated. The same was true of group ND-D. Throughout the remainder of the study, group ND-ND performed significantly better than all the other groups. The performance of group D-NDA gradually improved over a period of about 10 weeks and eventually surpassed their performance during the first 10 weeks of the study. Group D-NDG showed a decrease in performance during drug withdrawal, but the level of performance recovered much faster than was observed in group D-NDA. Group ND-D's performance, after an initial decrease, rapidly recovered to a level comparable to that observed during the first 10 weeks. Group D-D's performance remained fairly constant throughout the entire study and in the final weeks of the study was lower than the performance of all the other groups.

Both drug discontinuation and initiation disrupted performance. The most severe and longest lasting deficits were produced by abrupt withdrawal. The group that did not receive drugs at any time during the study (ND-ND) performed superior to all of the other groups.

The results of these four studies taken collectively indicate that neuroleptic drugs administered to institutionalized mentally retarded individuals 1) in many instances do not reduce inappropriate behaviors; 2) interfere with responding to reinforcement contingencies; and 3) interfere with the performance of workshop tasks. These effects are observed in both responders and nonresponders. Given the results of the above studies and other published reports (e.g., Breuning, Ferguson, & Cullari, 1980), it is apparent that the possible deleterious effects of neuroleptic drugs must be carefully assessed before they are administered to mentally retarded individuals. Finally, the results of these studies have possible legal ramifications. It is stated in the *Minimum Constitutional Standards for Adequate Habilitation of the Mentally Retarded* that neuroleptic drugs will not be used "...in quantities that interfere with a residents, habilitative *program*..." The interpretation of these standards with regard to drug responders is complex; since inappropriate behaviors are being effectively controlled there is no problem concerning excessive doses, but it is obvious that even with these individuals drugs interfere with habilitative processes. The case against the use of these drugs with nonresponders is very clear. When there is no evidence of a therapeutic effect and habilitative processes are clearly interfered with, neuroleptic drug use should be considered excessive and unnecessary.

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An Applied Dose-Response Curve of Thioridazine with the Mentally Retarded: Aggrssive, Self-Stimulatory, Intellectual, and Workshop Behaviors—A Preliminary Report[1]

Stephen E. Breuning, Ph.D.[2]

Neuroleptic drugs are frequently prescribed for the mentally retarded in an attempt to suppress a plethora of unwanted behaviors. Surveys spanning the past decade have consistently shown that 40-50% of the institutionalized mentally retarded receive such drugs (*see* Breuning & Poling, in press, for a review). Most recently it has been found that similar use of neuroleptic drugs occurs in community foster homes and group homes for the mentally retarded (i.e., Davis, Cullari, & Breuning, in press). In both institutional and community settings thioridazine is by far the most prescribed neuroleptic with this population, as it accounts for 60-70% of all neuroleptic drug prescriptions.

Despite its wide use, little is known about the therapeutic and contratherapeutic effects of thioridazine. In three recent reviews it was concluded that thioridazine *may* be useful in reducing aggression, general motor activity, and self-stimulation with the mentally retarded (Aman, in press; Breuning & Poling, in press; Ferguson & Breuning, in press). However, these reviews also point out that evidence of therapeutic effect is the exception, not the rule, with thioridazine and the mentally retarded. The issue of therapeutic effect is further confounded by data from several recent reports which suggest that even when there is a reduction in symptomatology, there may well be a concomitant reduction or disruption (increased variability) in adaptive/habilitative behaviors (e.g., Breuning & Davidson, 1981; Breuning, O'Neill, & Ferguson, 1980; Singh & Aman, 1981).

While these findings have consistently been replicated in methodologically sound studies, only one study (Singh & Aman, 1981) has attempted to examine thioridazine effects in a dose-dependent manner. It was found that a low dose of thioridazine was as effective as a much larger dose in controlling self-stimulatory behaviors. The present report represents the initial findings of a study designed to further the findings of Singh and Aman (1981) by assessing the dose-response properties of thioridazine with mentally retarded individuals across four response measures, nine dose levels, and a placebo condition.

Method

Subjects

The subjects were 84 non-autistic, institutionalized, mentally retarded individuals between the ages of 13 and 27 and with IQs ranging between 34 and 59. Informed consent was obtained for each subject and there were approximately equal numbers of males and females. In total, there were 14 responders and 14 nonresponders assessed for aggressive behaviors, and 16 responders and 16 nonresponders assessed for self-stimulatory behaviors. For the intellectual and workshop behaviors there were 14-14 and 15-15 responders and nonresponders, respectively. Most of the individuals being assessed for the aggressive or self-stimulatory behaviors were also individuals receiving either the intellectual or workshop tasks. There were no individuals assessed on both adaptive measures, and those assessed for aggressive behaviors were not emiting self-stimulatory behaviors and vice versa.

Procedure

Each dose and placebo condition lasted for 8 weeks with half of each group (e.g., 7 of 14 responders) receiving conditions in an ascending order and half in a descending order (8-7 or 7-8 for workshop). Because of the clinical nature of the study, these subject assignments were not prepared randomly. Rather, half of the subjects had reached the highest dose as part of clinical treatment and were now withdrawn. The remaining half were determined clinically appropriate for initiation of neuroleptic treatment because of the above-mentioned symptomatology. Double-blind conditions were in effect throughout, as neither

[1]This study was supported in part by USPHS Grant MH-32206 from the National Institute of Mental Health.

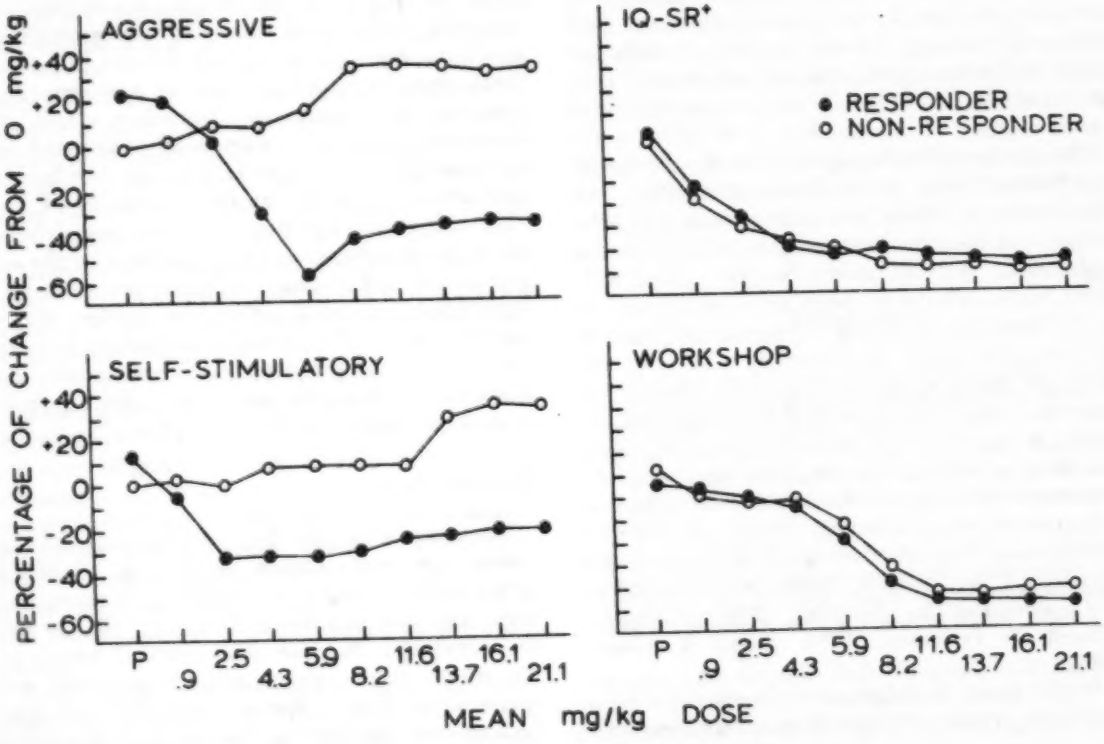
[2]Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, PA 15261.

staff nor subjects were aware of conditions or dose. There were two equal dose administrations daily.

Definitions of aggression and self-stimulation were in observable and measurable terms and recorded by staff in 30-minute intervals, 24 hours per day (*see* Breuning, O'Neill, & Ferguson, 1980). Reliability checks were made by independent observers on a random selection of four 30-minute intervals per day. Mean reliability was 87.4% with a range of 76.3% to 92.4% across days. Intellectual behaviors were assessed using the procedure described by Breuning and Davidson (1981). Briefly, subjects received intellectual testing (Stanford-Binet, Form LM) under conditions where correct responses were reinforced with edible reinforcers selected on an individual basis. Workshop behaviors were assessed using procedures described by Davis, Poling, Wysocki, and Breuning (1981). In short, the number of 15-part coaster bicycle brakes (Bendix RB-2) assembled on an individual basis were counted. Completion of 0-7 of the 15 parts counted as 0 completion, 8-14 of the parts as one-half completion, and 15 parts as one completion.

Results and Discussion

The Figure shows the results from each response measure separately for responders and nonresponders. Data were analyzed using split-plot analyses of variance (one per response measure) with repeated measures and *post hoc* comparisons following Tukey's honestly significant difference (HSD) method (*see* Kirk, 1968).



FIGURE

Percentage of change from the off-drug condition (O mg) plotted separately for responders and nonresponders and each response measure across the placebo condition (P) and nine doses.

Data in the Figure are plotted as percentage of change from the off-drug condition (0 mg) across the placebo (P) condition and nine doses. Data for the aggressive and self-stimulatory behaviors reflect daily frequencies; intellectual behaviors (IQ-SR+) reflect intelligence test scores; and workshop behaviors reflect the number of parts completed per session. Dose levels are plotted as means with no subject having more than a + or − 4% deviation from the mean.

For the responders, a dose of 5.9 mg/kg/day was optimal for reducing aggressive behaviors and a dose of 2.5 mg/kg/day was optimal for reducing self-stimulatory behaviors ($p < .01$). Higher doses had little additional effect except for a loss of behavioral control; i.e., increased frequencies of target behaviors ($p < .01$). For the nonresponders, the frequencies of aggressive and self-stimulatory behaviors showed no substantial changes at the lower doses ($p > .05$) but began to worsen as thioridazine doses increased ($p < .01$). For both responders and nonresponders, there were significant decreases in intellectual and workshop behaviors at even low doses ($p < .01$) and a continued worsening as the dose was increased ($p < .01$). Performance in the IQ-SR+ task was substantially more sensitive to dose changes than with the workshop task. For all response measures and both responders and nonresponders, identical dose effects were obtained regardless of ascending or descending order of conditions ($p > .05$).

The results from this study are clear. Mentally retarded individuals showing a beneficial response to thioridazine treatment (responders) will likely have the greatest suppression of aggressive behaviors occur at a moderate dose (about 6.0 mg/kg/day) and the greatest suppression of self-stimulatory behaviors occur at a fairly low dose (about 2.5 mg/kg/day). Regardless, it is also likely that there will be a concomitant decrease in adaptive/habilitative behaviors. For nonresponders, there may not only be a failure to show suppressed inappropriate behaviors but also a worsening of these behaviors (behavioral toxicity) along with a decrease in adaptive/habilitative behaviors.

There are two additional points worth making. First, preliminary correlational and discriminant function analyses show no significant relationship between psychiatric diagnosis or other possible predictor variables and whether or not an individual was a responder or nonresponder. Second, the equal numbers of responders and nonresponders in this study should not be interpreted to mean that 50% of the mentally retarded receiving neuroleptics will be responders. The reviews cited earlier suggest that only 10-15% of the mentally retarded receiving a neuroleptic will show a beneficial response.

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An Analysis of Institutionalized Retarded Residents Using DIS-CO[1]

Robert L. Sprague, Ph.D.[2]

It is likely that tardive dyskinesia is as common among institutionalized populations of mentallyretarded peoples, due to extensive use of neuroleptic drugs (Davis, Cullari, & Breuning, in press; Sprague, 1977), as it is in psychiatric populations of patients. No systematic assessment using standardized instruments of such a population has been conducted, although surveys have been made (Baldessarini, 1979; Paulson, Rizvi, & Crane, 1975). In addition to the usual complications that persistent tardive dyskinesia causes any person, recent research has shown that even mild to moderate dyskinesia can interfere with performance on sheltered workshop tasks in which a large percentage of retarded residents participate as a therapeutic program (Breuning, Davis, Matson, & Ferguson, in press). When the fact that a serious side effect also actively interferes with ongoing programs is brought to the attention of a court, the court usually issues orders restricting use of such drugs (Sprague, in press).

Considering these two issues solely, the time for a systematic investigation of tardive dyskinesia in institutionalized populations of mentally retarded residents is long overdue. With these aims in mind, a project was undertaken to systematically assess the populations of two state-operated institutions for the mentally retarded in the midwest. In one institution it was possible to assess each resident, but in the other institution numerous problems such as budget cuts reducing staff and resignations prevented assessing the entire population. Consequently, emphasis is given in this report to the first institution in which the entire population of 519 residents participated in the study with less emphasis on the second facility where 67 residents were studied for a total of 586 residents.

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[2]Institute for Child Behavior and Development, University of Illinois, Champaign, IL 61820.

Note: Anyone wishing a copy of the DIS-CO Scale should write to the author at: Institute for Child Behavior and Development, University of Illinois, 51 E. Gerty Drive, Champaign, IL 61820.

A survey of the literature on rating scales of dyskinesia revealed that only one instrument, the Abnormal Involuntary Movement Scale (AIMS), had some reliability and validity data (Smith, Kucharski, Eblen, et al. 1979; Smith, Kucharski, Oswald, & Waterman, 1979), but it was felt that the items were of such a global nature that one might not be able to distinguish between tardive dyskinesia and the numerous movement disorders due to neurological disease, brain damage, and long-term social isolation, problems which can be readily found in institutionalized populations. Thus, a new scale was developed which contained 34 items subdivided into 10 body areas. Because the scale is too long to publish in this journal, copies are available from the author. Preliminary pilot studies were conducted on the wording of items which were changed to be readily understandable to nurses and licensed practical nurses. The scale was given the name Dyskinesia Identification System-Coldwater (DIS-CO).

After intensive inservice training and pilot ratings on some residents, nurses at one institution were asked to personally examine and rate every resident in the institution. Where possible, i.e., two nurses familiar with the residents in a ward, two independent assessments of the same residents were made to obtain interrater reliability correlations. Also, when possible, two different assessments about 1 month apart by the same nurse for the same resident were made to obtain stability correlations.

Each item was rated on a five-point scale: not present - 0, minimal - 1, mild - 2, moderate - 3, and severe - 4 with NA (not assessed) used when it was not possible to rate that particular item.

In the Table are listed the means and standard deviations for each of the 10 body areas with the number of items per body area in parentheses, the reliability correlation between two independent raters, and the stability correlations over about a 1-month period of time. Totals for each body area were summed over the number of items for that area to obtain the data included in the Table. In a similar fashion, the overall total was obtained. The overall mean rating was 8.8 (possible range 0 to 132) with a standard deviation of 6.8. All of the reliability and stability correlations are highly significantly different from zero.

Table

Means and Standard Deviations for Each Body Area and Interrater and Stability Correlations for One Institution

Body Region (number of items)	N	Descriptive Mean	SD	N	Reliability Correlation	N	Stability Correlation
Face (2)	519	1.1	1.3	177	.61†	160	.55†
Ocular (2)	519	.6	1.0	177	.64†	160	.48†
Oral (8)	517	2.2	2.6	177	.79†	160	.48†
Lingual (8)	428	2.0	2.7	177	.84†	160	.68†
Head/neck (2)	516	.3	.8	177	.48†	160	.52†
Trunk (2)	475	.2	.5	177	.21*	160	.31†
Upper limb (4)	513	1.6	1.9	177	.67†	160	.71†
Lower limb (4)	318	1.3	1.6	177	.67†	160	.45†
Gross body (1)	487	.2	.6	169	.14*	147	.15*
Ambulation (1)	343	.5	1.0	133	.41†	116	.64†
TOTAL (34)	519	8.8	6.8	177	.78†	160	.77†

*Significant at $p < .005$
†Significant at $p < .001$

It should be obvious that this reported data represents only the first step of a project if tardive dyskinesia is to be accurately and reliably assessed repeatedly in retarded populations and its relationship to neuroleptic drug administration determined. The DIS-CO instrument will be refined on the basis of this data, the refined instrument related to 4 years of drug history now available on the residents and, finally, a withdrawal of neuroleptic drugs study is underway to ascertain the effects of withdrawal on the ratings of abnormal movement as shown by this scale. Clearly, much remains to be done, but the issues are crucial to the welfare of mentally retarded people.

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Tardive Dyskinesia in Mentally Retarded Children, Adolescents, and Young Adults: North Carolina and Michigan Studies

C. Thomas Gualtieri, M.D.,[1] Stephen E. Breuning, Ph.D.,[2] Steven R. Schroeder, Ph.D.,[2] and Dana Quade, Ph.D.[2]

Although neuroleptic drugs are frequently prescribed for behavior control and alleviation of psychiatric symptoms in mentally retarded children, adolescents, and young adults (Lipman, DiMascio, Reatig, & Kirson, 1978; Davis, Cullari, & Breuning, 1982), no systematic or methodologically acceptable studies of the occurrence of tardive dyskinesia (TD) in mentally retarded patients have appeared in the literature (Gualtieri & Hawk, 1980). Two parallel studies of TD and other problems associated with neuroleptic withdrawal were conducted: the North Carolina study (Gualtieri and Schroeder) was primarily concerned with clinical factors associated with TD; the Michigan study (Breuning) was primarily concerned with the course of TD symptoms after neuroleptic withdrawal.

Method

Subjects

Subjects were referred by treating physicians who felt that a trial neuroleptic withdrawal should be a routine part of each patient's clinical management. Inclusion criteria were: a) IQ less than 75, functional diagnosis of mental retardation (American Association of Mental Deficiency criteria); b) stable living environment; c) appropriate educational or workshop placement; d) good general health, with no active neurologic disease, or history of neurologic disorder which might be associated with dyskinesia; and e) continuous neuroleptic treatment of at least 6 months' duration.

[1]Biological Sciences Research Center, Department of Psychiatry, and the Department of Statistics, University of North Carolina, Chapel Hill, NC 27515.

[2]Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, PA 15261.

North Carolina Study. Thirty-eight subjects (age 5 to 47, mean = 19.4 ± 1.7 [SEM]) were studied at four clinical sites: a psychiatric hospital, a pediatric psychopharmacology clinic, and two residential facilities for the mentally retarded. The mean age at which subjects began neuroleptic treatment was 10.9 (± 1.0) years. The mean duration of treatment was 8.3 (± 6) years, and total lifetime exposure to neuroleptics, expressed in chlorpromazine (CPZ) equivalents (Davis, 1976) ranged from 13.5 to 11,188 grams (mean = 1,046.7 ± 344.3).

Michigan Study. Fifty-seven subjects were studied at the Coldwater Regional Center. Subjects in the Michigan study were older than the North Carolina group ($p < .02$), had higher IQ scores ($p < .001$), and were treated with higher neuroleptic doses immediately prior to withdrawal ($p < .001$) (*see* Table). Because so many subjects in the Michigan group had been treated with neuroleptics for substantial periods of time as outpatients, comprehensive neuroleptic drug histories are not available for this group. All subjects, however, had been treated continuously with neuroleptics for at least 1.3 years prior to entry into this study.

Procedure

Subjects received comprehensive neurologic and developmental assessments prior to neuroleptic withdrawal. Special attention was given to neurologic or developmental problems (e.g., cerebral palsy, autism) which might be associated with dyskinetic movements, stereotypies, or psychotic mannerisms which may have anteceded neuroleptic treatment. After baseline evaluation, subjects were withdrawn from neuroleptic drugs, with serial examinations for dyskinesia, behavior change, or nondyskinetic withdrawal symptoms.

North Carolina Study. Subjects were assessed at weekly or biweekly intervals at baseline, during and after withdrawal, and until 8 weeks after complete discontinuance of neuroleptics. The Abnormal Involuntary Movement Scale (AIMS) exam and rating scale were used (Guy, 1976). Subjects who continued to manifest dyskinesia at 8 weeks were subsequently reexamined at monthly intervals. Mean interrater reliability among three physician raters on the AIMS rating scale was 0.83 (0.74-1.00) (Cohen's Kappa).

Table

Demographic and Outcome Data

	N.C.	Mich.	Total
N	38	57	95
Sex: Male	28	28	56
Female	10	29	39
Age (Yrs) (Mean ± *SD*)	19.4 ± 10.3	25.7 ± 12.6	
Age Range	5-47	12-71	5-71
IQ	31.2 ± 15.9	40.4 ± 14.8	
IQ Range	9-69	14-74	9-74
Drugs: Thioridazine	28 (74%)	27 (47%)	55 (58%)
Other neuroleptics	10	30	40
Mean Daily Dose (CPZ* equivalents)	239.9 ± 293.8 48.3(SEM)	688.6 ± 310.2 41.1	
Outcome:			
No problems	12 (32%)	19 (33%)	31 (33%)
Withdrawal-related problems	13 (34%)	20 (35%)	33 (35%)
Tardive dyskinesia	13 (34%)	18 (32%)	31 (33%)
Mild	5 (13%)	3 (5%)	8 (8%)
Moderate-severe	8 (21%)	15 (26%)	23 (24%)
Maintenance onset	3 (8%)	4 (7%)	7 (7%)

*Chlorpromazine

Michigan Study. Dyskinetic movements were assessed at weekly intervals at baseline, during withdrawal, and for 80 weeks thereafter. The Withdrawal Emergent Symptom Checklist (WESC) rating scale and examination were used (Engelhardt, 1974). and interrater reliability was 0.79 (Cohen's Kappa).

Results

Four outcome categories were considered according to diagnostic criteria that have been described elsewhere (Gualtieri, Sprague, Breuning, & Campbell, 1981): 1) no problems associated with neuroleptic withdrawal; 2) transient withdrawal problems, that is, withdrawal dyskinesia, nondyskinetic withdrawal symptoms, or acute behavior deterioration; beginning during neuroleptic withdrawal or immediately thereafter, and lasting less than 16 weeks after complete withdrawal; 3) mild TD; and 4) moderate or severe TD. In spite of the clinical differences between the two groups, the outcome of both studies are remarkably similar (*see* Table).

One-third of the total group ($N = 95$) experienced no problems prior to, during, or for at least 8 weeks after neuroleptic withdrawal; one-third experienced only transient withdrawal-related problems; and one-third had TD. Most of the cases of TD were characterized by moderate or severe movements. Of 31 cases of TD, only 7 were apparent while patients were on maintenance doses of neuroleptics. Six of the 7 cases of maintenance onset TD were characterized by dyskinesia that was rated as moderate or severe.

Thioridazine (THD) was the neuroleptic most commonly prescribed in both locations (58% of subjects). There was no association between the use of THD or any other particular neuroleptic and the development of TD.

North Carolina Study

The following were considered in a stepwise regression analysis of variables which might be associated with the development of moderate to severe tardive dyskinesia: location, age, race, sex, age at which neuroleptic treatment was begun, IQ, duration of treatment, total lifetime neuroleptic exposure, mean daily dose, and use of THD as the primary neuroleptic. The single variable that was most highly correlated with the development of moderate or severe TD was total lifetime exposure (analyzed as log of the total lifetime dose, $R^2 = 0.38$ for a one-variable regression). The regression analysis selected three independent variables, total lifetime exposure (log dose), IQ, and the age at which neuroleptic treatment began that were most highly correlated with moderate or severe TD ($R^2 = 0.65$, $F = 18.82$, 3 and 31 *df*), and each independent variable contributed significantly to the regression. Since treatment duration was highly correlated with total lifetime exposure ($r = +0.69$) adding it to the analysis did not increase R^2. None of the other variables contributed significantly to the equation. Nonparametric correlations (Goodman-Kruskal) also showed total lifetime exposure to be the variable most highly correlated with TD ($G = .531 \pm .120$, $p < .0001$).

Michigan Study

Dyskinetic movements were maximal at 4 weeks after neuroleptic withdrawal, when 36 of 57 patients (63%) exhibited symptoms. Dyskinetic movements were noted in 30 patients (53%) at 16 weeks, and in 18 patients (32%) at 52 and 80 weeks. This remission pattern was similar for movements of the tongue, lips and face, and head, limbs, and trunk. Facial dyskinesias which were rated as mild at 4 weeks were more likely to remit, and those which were rated as moderate or severe at 4 weeks were more likely to persist at 80 weeks (chi-square analysis, $p \leq .05$ and $\leq .025$, respectively). Dyskinetic movements which were apparent prior to neuroleptic withdrawal were invariably persistent.

Discussion

Moderate to severe, persistent TD is a cause for concern and a serious problem in mentally retarded children, adolescents, and young adults treated with neuroleptic drugs, a finding that must stand in sharp contrast to the dearth of empirical data to support the clinical use of neuroleptics in this group. The occurrence of TD is, not surprisingly, related to the patient's total lifetime exposure to neuroleptics. Dyskinetic movements that "break through," i.e., that are manifest on maintenance neuroleptic doses, predict a particularly severe and persistent course. However, the large majority of cases of TD — even severe and persistent TD — may not be apparent while patients continue to receive neuroleptic drugs. One may surmise, then, that epidemiologic surveys of TD that do not include trial neuroleptic withdrawal periods will necessarily underestimate the frequency of TD. On the other hand, a substantial number of the dyskinetic movements which arise within 4 weeks of neuroleptic withdrawal will remit spontaneously; such cases are better classified as "withdrawal dyskinesias."

Clearly, although advanced age may increase the risk of TD (Smith & Baldessarini, 1980), youth, at least in combination with mental retardation, does not confer protection from TD. In light of this serious risk, it is noteworthy that very few of the patients in these two samples actually needed to be on neuroleptic medication. In the North Carolina group, only 11 of 38 patients had to return to neuroleptic treatment; in the Michigan group, none returned. When behavior problems following neuroleptic withdrawal did arise, they were usually time limited, or readily controlled using behavioral or programmatic approaches. Many of these behavior problems appeared to be concentrated in the immediate postwithdrawal period, suggesting that a period of behavioral instability occurs following withdrawal. Physicians who withdrew mentally retarded patients from neuroleptic drugs should not take this postwithdrawal behavior deterioration as a mandate to immediately resume treatment with neuroleptics.

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Neuroleptic Serum Levels in Mentally Retarded Boys

James C. Harris, M.D.,[1] Larry E. Tune, M.D.,[1] Michael Kurtz, M.D.[2] and Joseph T. Coyle, M.D.[1]

This is a preliminary report on the measurement of serum neuroleptic levels in mentally retarded children and adolescents. The investigators have measured neuroleptic levels in 60 patients on a variety of neuroleptics (haloperidol, chlorpromazine, trifluoperazine, molindone, thioridazine). However, a summary of neuroleptic blood levels in 9-15 year-old boys taking thioridazine for behavior management is the subject of this report.

[1]The Johns Hopkins University School of Medicine and Hospital, Baltimore, MD 21205.

[2]The University of Pennsylvania School of Medicine, Philadelphia, PA 19104.

Until recently there had been no simple procedure for the measurement of neuroleptic serum activity levels. However, a radioreceptor assay described by Snyder and Creese (1977) based on competition of neuroleptics in plasma or serum for the binding of [^{3}H]-spiroperidol to dopamine receptors may serve this function. The assay measures dopamine receptor blockade and, therefore, detects active metabolites as well as parent drug activity. This is a distinct advantage for thioridazine which has several active metabolites.

Previous reports by Tune, Creese, Depaulo, Slavney, Coyle, and Snyder (1980) and Cohen, Lipinski, Pope, Harris, and Altesman (1980) have demonstrated a correlation between serum levels of neuroleptics and therapeutic response in acutely psychotic patients during an acute episode. Both studies showed poor correlations between oral dosage and serum level.

Myers, Tune, and Coyle (1980) have used this assay to manage schizophrenia in childhood at Johns Hopkins. The current investigators are now studying the use of the radioreceptor assay in the retarded where both thioridazine and haloperidol are approved for use in the management of behavior disorders.

Method

Sixteen moderately to severely retarded 9-15 year-old boys taking thioridazine as a single treatment participated in the study. All are residents in a well-staffed and well-supervised behaviorally oriented institutional setting and are considered to be patients who are the most difficult to manage. Each subject had been on the same dosage of medication for at least 2 weeks.

Five milliliters of blood were drawn from each member of the study population 2 hours after supervised oral administration of the medication to obtain peak blood levels. Specimens were cooled and allowed to clot over a 2-hour period, centrifuged, and the serum frozen at 70° C in glass tubes. Assays were performed in triplicate.

On the day before the blood specimen was obtained, the Sprague Resident Behavior Checklist was completed by the case manager.

Results

The serum drug levels were looked at as total dosage and as mg/kg/day. Drug levels were recorded as haloperidol equivalents (ng/ml). In each instance, when a resident was on a given daily dosage of drug there was variability in blood level at that dosage. Thus, for the four residents on a total daily dosage of 50 mg, levels ranged from 13-102 ng/ml haloperidol equivalents and for the four residents on 75 mg/day the range was from 37-199 ng/ml haloperidol equivalents. In two residents on 100 mg/day, the range was from 65-122 ng/ml haloperidol equivalents. So, on a given dose there was up to an eightfold variation in drug level.

If the dosage is looked at as mg/kg of thioridazine, when the dosage reached 2.0 mg/kg considerable variability in level was evident. For example, at a dosage range of 2.0-2.3 mg/kg the level varied from 20-199 ng/ml haloperidol equivalents, a tenfold difference in level. The four residents on higher dosages from 3.2-14.8 mg/kg had levels over 95 ng/ml haloperidol equivalents.

The Sprague Resident Behavior Rating Scale was completed on each resident. No specific correlations were demonstrated between drug level and total score or individual scores on specific behavioral items. Since intense aggression and assaultive behavior is a common indication for drug treatment, global ratings of aggression were reviewed carefully. There was no correlation between drug level and severity of aggressive behavior, although the most physically aggressive boys were on the highest dosages of neuroleptics, 4.8 and 8.8 mg/kg, respectively.

Conclusions

In this group of retarded boys we have demonstrated variability in the neuroleptic level of thioridazine 2 hours after oral administration, as was previously reported in adults by Tune et al. (1980) and Cohen et al. (1980). Further work will need to be done to demonstrate the usefulness of the assay in patient management and to determine whether there is a threshhold neuroleptic level in the management of target symptoms in the retarded, especially in aggressive behavior. However, current findings may be pertinent to the possible relationship of high neuroleptic levels and long-term complications such as dyskinesias and for thioridazine, retinopathy.

The assay may provide a useful tool for future monitoring of drug therapy in the retarded and be of use in the treatment of medication nonresponders.

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Free Communications—Session A

Chair: **Eugene S. Paykel, M.D.**
Department of Psychiatry
St. George's Hospital
Medical School
London, England

and

Paul D. Leber, M.D.
Division of Neuropharmacological
Drug Products
Food and Drug Administration
Rockville, Maryland

• An Open, Uncontrolled Clinical and Pharmacokinetic Study with LM 5008: A New Antidepressant
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New York State Psychiatric Institute, New York, NY

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New York State Psychiatric Institute and Columbia Presbyterian Medical Center, New York, NY

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New York State Psychiatric Institute, New York, NY

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Texas Research Institute of Mental Sciences, Texas Medical Center, Houston, TX

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Long Island Jewish-Hillside Medical Center, Glen Oaks, NY

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Rockland Research Institute, Orangeburg, NY; New York University and Columbia University, New York, NY; and New York Medical College, Valhalla, NY

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New York University, Ward's Island and New York, NY

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Henry A. Nasrallah, Robert E. Smith, Frederick J. Dunner, and Mona McCalley-Whitters
VA Medical Center and University of Iowa College of Medicine, Iowa City, IA

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Murray Alpert, Florence Diamond, and Arnold J. Friedhoff
New York University Medical Center, NY

Efficacy of Mianserin in Mildly Depressed Patients

Jonathan W. Stewart, M.D.,[1] Frederic M. Quitkin, M.D.,[1] Patrick J. McGrath, M.D.,[1] Michael R. Liebowitz, M.D.,[1] and Donald F. Klein, M.D.,[1]

Mianserin is a tetracyclic antidepressant with demonstrated efficacy (Brogden, Heel, Speight, & Avery, 1978). Since mianserin appears to have a different mechanism of action from the tricyclic antidepressants (TCAs)(Brogden et al., 1978), it seemed useful to investigate the efficacy of mianserin in patients with relatively mild depression, a population similar to that previously studied using desipramine (DMI) (Stewart, Quitkin, Liebowitz, et al., 1981.)

The study design was identical to that previously utilized for DMI (Stewart et al., 1981). Basically, patients aged 18-65 with Hamilton Depression Scores (HAM-D) less than 19 who met Research Diagnostic Criteria (RDC) (Spitzer, Endicott, & Robbins, 1978) for depression were placed on placebo for 10 days single-blind. Patients who responded were removed from further study. Those who maintained their level of depression were randomized to double-blind treatment with mianserin or placebo for 6 weeks. At reevaluation after 10 days of placebo and after 6 weeks' double-blind treatment, response was defined as a Clinical Global Impression (CGI) score of 1 or 2 ("very much improved" or "much improved"). Nonresponse was a CGI score of 3 or higher ("minimally improved," "unchanged," or "worse").

Initial mianserin dose was 30 mg/d, increased twice weekly to 150 mg/d unless side effects prevented such regular increases. Previous studies had used 60-90 mg/d as a maximal dose of mianserin (Coppen, Ghose, et al., 1977; Wheatley, 1977). As this dose of mianserin had been compared with 150 mg/d of amitriptyline, it was felt that a higher dose of mianserin might be more comparable to 300 mg of a TCA. In addition, a pilot study (McGrath, Quitkin, Stewart, et al., 1981) had suggested additional benefit as dose was raised to 150 mg/d. Hence, the latter was selected as a maximal dose to attempt to maximize likelihood of response. Statistical analysis included the chi-square test without Yates correction to 2×2 tables using two-tailed tests.

The mean age of 127 patients entering the study was 43 ± 12 (range, 21-65). There were 72 men and 55 women. Twenty-seven patients dropped out and 17 responded during the initial 10 days of placebo. Of the 83 patients completing the randomization trial, 54% (21/39) responded to mianserin, 27% (12/44) to placebo ($X^2 = 6.64$, $p < .02$). According to RDC diagnoses, patients with definite diagnosis for major depressive disorder demonstrated a 50% (10/20) response to mianserin, 14% (3/22) to placebo, a statistically significant difference ($X^2 = 6.48$, $p < .02$). Patients with intermittent depressive disorder did not demonstrate this difference, 64% (7/11) responding to mianserin, 40% (4/10) to placebo

[1]New York State Psychiatric Institute, New York, NY 10032.

($X^2 = 1.17$, n.s.). There were not enough patients with minor depressive disorder ($N = 6$) to test for significance.

Differential response among RDC major depressives was entirely accounted for by those with endogenous subtype. Thus, patients with endogenous subtype had a 77% (10/13) response to mianserin, 9% (1/11) to placebo ($X^2 = 11.50$, $p < .001$). By contrast, major depressives without endogenous depression had an 18% (2/11) response to mianserin, 31% (5/16) to placebo ($X^2 = 0.58$, n.s.). Major depressives with endogenous depression were significantly more likely to respond to mianserin than major depressives without endogenous subtype ($X^2 = 8.22$, $p < .01$).

Most of the subtypes of major depressive disorder which had appreciable numbers demonstrated at least a trend for significant drug-placebo response differences. In each case, however, this difference seemed entirely accounted for by those who also had endogenous subtype. For example, among major depressives with simple subtype, 50% (9/18) improved on mianserin, 14% (3/21) on placebo ($X^2 = 5.80$, $p < .02$). However, patients with simple subtype who also had endogenous subtype had an 82% (9/11) response rate to mianserin, 9% (1/11) to placebo ($X^2 = 11.73$, $p < .001$). Patients with simple subtype who did not meet criteria for endogenous had a 0% (0/7) response to mianserin, 20% (2/10) response to placebo ($X^2 = 1.59$, n.s.). Response to mianserin was significantly more likely among the simple subtype if they were also endogenous than if not ($X^2 = 11.45$, $p < .001$).

Among patients with situational subtype of major depression, 30% (6/20) improved on placebo. While this was not significantly greater than placebo response of major depressives without situational subtype (13%, 1/8, $X^2 = 0.9$, n.s.), this had been the group in the previous study (Stewart et al., 1981) which demonstrated increased response. Combining placebo responses from the two studies yielded a significantly increased placebo response among major depressives with situational subtype when compared to those without situational subtype ($X^2 = 7.13$, $p < .05$, $df = 2$).

Regardless of diagnosis, differential response occurred among patients with more severe illness. That is, patients at or above the median Day 10 HAM-D score of 13 had a 60% (12/20) response to mianserin, 27% (7/27) to placebo ($X^2 = 5.54$, $p < .02$). Patients with Day 10 HAM-D score below 13 had a 47% (9/19) response to mianserin, 29% (5/17) to placebo ($X^2 = 1.22$, n.s.).

These results demonstrate the efficacy of mianserin in this population of mild- to moderately depressed outpatients. In particular, patients with endogenous subtype of major depressive disorder seemed to account for the mianserin-placebo response difference found. Major depressives without endogenous subtype may do poorly on mianserin. No group was found to have increased placebo response. These differential responses according to RDC subtype partially validate this system as being useful for the treatment of affective illness.

Differential response according to presence or absence of endogenous subtype suggests that RDC major depression defines a heterogeneous population, some of whom improve due to specific mianserin effects, some who are unresponsive to this medication, and a few of whom improve due to nonspecific factors. For both research and clinical purposes, RDC major depression with endogenous subtype may define a fairly homogeneous population in which to use mianserin.

Although placebo response of major depressives with situational subtype was not significantly greater than those without situational subtype, combining these results with those from the previous study (Stewart et al., 1981) did suggest increased placebo response among situational depressives. This again suggests that some patients with clear-cut psychosocial precipitants may improve without the need for medication.

While many of these results were similar to those found previously with DMI, mianserin may not have the same spectrum of action as DMI. In the present study, 65% (7/11) of patients with intermittent depressive disorder responded to mianserin. While this was not significantly greater than the placebo response in this group, it does compare favorably with the 13% (1/8) response rate of this group to DMI in the earlier study. Since placebo response in this group was little different in the two studies (4/11 vs. 2/8), this suggests that mianserin might be beneficial for some intermittent depressives, while DMI is not.

As in the DMI study (Stewart et al., 1981) it

TABLE

Response by Diagnosis and Severity of Illness

Research Diagnostic Criteria**	% Response to Mianserin	% Response to Placebo	χ^2	Significance
Major Depressive Disorder	50 (12/24)*	23 (7/31)	4.50	$p < .05$
with endogenous subtype	77 (10/13)[a]	13 (2/15)	11.50	$p < .001$
without endogenous subtype	18 (2/11)[a]	31 (5/16)	0.58	n.s.
Simple subtype	50 (9/18)	14 (3/21)	5.80	$p < .02$
with endogenous subtype	82 (9/11)[b]	9 (1/11)	11.73	$p < .001$
without endogenous subtype	0 (0/7)[b]	20 (2/10)	1.59	n.s
with situational subtype	36 (5/14)	30 (6/20)[c]	0.12	n.s.
without situational subtype	63 (5/8)	13 (1/8)[c]	4.27	$p < .05$
Minor depressive disorder	67 (2/3)	33 (1/3)	—	—
Intermittent depressive disorder	64 (7/11)	36 (4/11)	1.64	n.s.
Severity of Illness				
Day 10 Hamilton ≥ 13	60 (12/20)	27 (7/27)	5.54	$p < .02$
Day 10 Hamilton < 13	47 (9/19)	29 (5/17)	1.22	n.s.
TOTAL	54 (21/39)	27 (12/44)	6.64	$p < .02$

*in parentheses are proportion responding.
**definite diagnoses only

Within Mianserin Contrasts:

a = Major Depressive Disorder with Endogenous Subtype vs. without Endogeneus Subtype, $\chi^2 = 8.22$, $p < .01$.
b = Major Depressive Disorder Simple Subtype with Endogenous Subtype vs. without Endogenous Subtype, $\chi^2 = 11.45$, $p < .001$.

Within Placebo Contrasts:

c = Major Depressive Disorder with Situational Subtype vs. without Situational Subtype, $\chi^2 = 0.93$, n.s.

was patients above the median of pre-randomization HAM-D scores who demonstrated specific medication response. This was true, however, only for Day 10 HAM-D, not for initial HAM-D (results not shown). Thus, patients who maintain their depression at a certain level for 10 days may be good candidates for either mianserin or DMI. Conversely, few patients with Day 10 HAM-D below 13 may be expected not to respond to either DMI or mianserin. Such patients may require other antidepressants, such as monoamine oxidase inhibitors, or psychotherapy in order to improve.

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The Effect of Mianserin on Cardiac Conduction: A Controlled Study

Patrick J. McGrath, M.D.,[1] Frederic M. Quitkin, M.D.,[1] David Blood, M.D.,[2] Michael R. Liebowitz, M.D.,[1] Jonathan W. Stewart, M.D.,[1] Abby Fyer, M.D.,[1] and Donald F. Klein, M.D.[1]

A variety of studies have shown that tricyclic antidepressants (TCAs) can affect the heart and particularly cardiac conduction at toxic dosages. The typical electrocardiographic (ECG) changes seen include tachycardia, prolongation of the PR interval, and widening of the QRS complex (Bigger, Kantor, Glassman, & Perel, 1978). These are associated with a variety of arrhythmias. The PR prolongation is thought to represent inhibition of conduction in the ventricular specialized conducting system, especially in the Bundle of His (Vohra, Burrow, Hunt, & Sloman, 1978). There is less clarity about how much effect the TCAs have on cardiac conduction when used at therapeutic dosage in the normal heart. In patients with preexisting conduction defects, there appears to be general agreement in the literature that the TCAs can aggravate these disturbances and cause significant cardiac toxicity (Kantor, Bigger, Glassman, et al. 1975). One of the features of interest of newer antidepressant compounds is the possibility of less cardiac toxicity. This is clinically important both because of the contribution this makes to the drugs' lethality in overdose as well as drug safety in patients with heart disease.

This investigation was undertaken to explore the cardiac effects of mianserin, a tetracyclic antidepressant. Crome and Newman (1977) reported a series of cases of poisoning with either maprotiline (Ludiomil) or mianserin (Bolvidon). In 20 cases of mianserin overdose, no arrhythmias similar to those seen in TCA overdose were observed. Kopera and Schenk (1977) monitored the clinical ECG of 54 patients who had preexisting "gravely disturbed" ECGs who were treated with 30 to 60 mg daily of mianserin. These studies suggested that mianserin had little or no cardiac toxicity.

[1]New York State Psychiatric Institute, New York, NY 10032.
[2]Columbia Presbyterian Medical Center, New York, NY 10028.

Method

Depressed patients between the ages of 18 and 65 with no significant medical illness were recruited from ongoing studies at the New York State Psychiatric Institute. All 48 patients had normal routine clinical ECGs. Each patient had a high-speed, high-fidelity ECG done while drug free. A second high-speed ECG was done after each patient was stabilized on drug or placebo treatment. These were recorded after 4 to 6 weeks of treatment after at least 1 week on the maximum dose of medication they received during the drug trial. Electrocardiograms were interpreted by an experienced cardiologist (D.B.) who was blind to treatment status of the patients. Statistical analysis was done using analysis of covariance with baseline scores as the covariate. Treatments were then compared by *t*-test.

Results

The mean daily drug dosages (mg/day) were 142 ± 16.9 for mianserin, 222 ± 71.2 for amitriptyline (AMI), and 225 ± 65.5 for imipramine (IMI)(*see* Table). Both AMI and IMI produced a significant increase in heart rate over baseline compared to placebo, while mianserin did not. The PR interval during drug treatment was significantly prolonged compared to placebo IMI but not for AMI, although there was a trend for the latter. Mianserin treatment did not

Table

Corrected ECG Variables by Treatment Compared to Placebo (Pre/Post Treatment Score)

	Placebo ($N = 12$)	Mianserin ($N = 19$)	Amitriptyline ($N = 9$)	Imipramine ($N = 2$)
Heart Rate (Beats/min)	70.9/72.5 -	77.8/79.8 N.S.	68.0/89.7 $p = .0003$	71.3/89.4 $p = .002$
PR Interval (msec)	148.3/144.4 -	147.8/149.5 N.S.	154.9/159.8 $p = .08$	145.3/161.9 $p = .0007$
QRS Interval (msec)	90.9/92.8 -	89.8/87.2 N.S.	83.7/91.7 $p = .04$	89.9/90.3 $p = .11$
QT Interval (msec)	418.3/427.0 -	427.8/430.3 N.S.	408.2/435.4 $p = .04$	431.2/445.8 $p = .05$

significantly change the PR interval. There was a trend for IMI to prolong the QRS interval, while mianserin and AMI did not. Prolongation of the QT_c interval was seen with AMI and IMI but not with mianserin treatment.

Conclusion

In a sample of medically healthy depressed patients with normal pretreatment ECGs treated with mianserin, no changes in cardiac conduction could be detected using high-speed, high-resolution ECG, compared to patients randomly assigned to placebo. Patients treated with IMI or AMI showed significant increase in heart rate as well as prolongation of the PR and QT_c intervals. The conduction changes, though clearly significant, would not have been demonstrated using routine clinical ECGs. The investigators conclude that mianserin, even when used in a dosage which is higher than has previously been employed clinically, shows little effect on cardiac conduction. If this is confirmed in further studies, trials of mianserin in depressed patients with disease of the cardiac conducting system would be warranted. If shown to be as effective an antidepressant as the tricyclics, it may be a drug of choice for patients with cardiovascular disease. Additionally, the method of high-speed ECG was suggested as being a sensitive screening technique to get evidence of the effects of new drugs on cardiac conduction in patients. This can be studied easily and evidence of the drug's effect shown, even though there are no clinically significant changes in the routine clinical ECG.

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Double-Blind Comparison of Bupropion vs. Amitriptyline in Depressed Out-patients

Nancy Harto-Truax, B.S.,[1] Judith Van Wyck Fleet, B.A.,[1] and Warren C. Stern, Ph.D.[1]

Bupropion HCl (Wellbutrin®) is a novel antidepressant with a structure shown in Figure 1. Potential antidepressant properties of bupropion were first suggested by its antagonism of tetrabenazine-induced ptosis and sedation in the mouse (Soroko, Mehta, Maxwell, et al. 1977). Bupropion's neurochemical and pharmacological profile is distinct from that of tricyclic and monoamine oxidase (MAO) inhibitor antidepressants. Bupropion has minimal effects on blocking neuronal reuptake of norepinephrine or serotonin, and does not inhibit MAO (Ferris, Maxwell, Cooper, & Soroko, 1981). Although bupropion weakly inhibits the reuptake of dopamine (Ferris et al., 1981), the neurochemical mode of the antidepressant action of bupropion must still be elucidated. In animals, bupropion does not possess anticholinergic, antihistaminergic, antiserotonergic, or cardiotoxic properties (Soroko et al., 1977; Wang, Parker, & Maxwell, 1981).

The antidepressant properties of bupropion were previously demonstrated in two double-blind, placebo-controlled inpatient trials (Stern & Harto-Truax, 1980). Bupropion produced significantly greater improvement than placebo starting at 8 days in one study (using doses of 300-750 mg/d) and at 3 weeks in the other study (doses of 300-450 mg/d). The side-effect profile of bupropion in both studies was similar to that of placebo with a notable absence of anticholinergic, cardiotoxic, or sedating side effects. In view of these initial efficacy findings and a low side-effect profile, it was appropriate to further assess the efficacy and safety of bupropion relative to a tricylic antidepressant.

In the present interim report, the antidepressant activity and safety of bupropion were compared to that of amitriptyline in a six-center out-

[1]Department of Clinical Research, Burroughs Wellcome Company, Research Triangle Park, NC 27709.

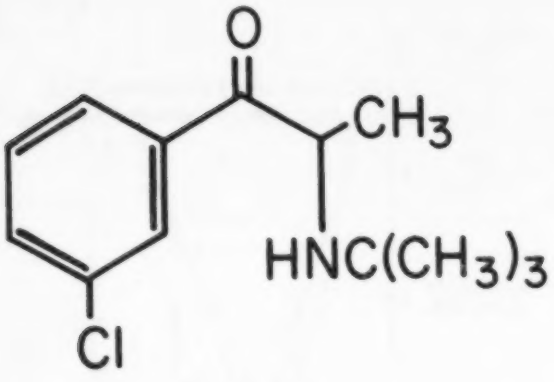

FIGURE 1. Structure of bupropion.

patient investigation (*see* Acknowledgments). A double-blind, randomized, parallel treatment design study with a 2:1 ratio of bupropion (N= 81) to amitriptyline (N= 42) treated patients was conducted. Treatment was scheduled for up to 15 weeks, the first week consisting of a single-blind placebo period. Responders to placebo during the initial week, as judged by an improvement of more than 10 points on the Hamilton Depression Scale or a Hamilton Depression rating of less than 18 on Day 7, were dropped from the study. Patients were then treated for up to 13 weeks with an ascending dosage regimen of either bupropion (300-450 mg/d, administered t.i.d.) or amitriptyline (75-150 mg/d, administered q.h.s.). The final week of the study consisted of a drug-free, posttreatment, followup period to assess possible withdrawal effects.

Entrance criteria required that each patient satisfy the diagnostic criteria for major affective disorder as defined by the FDA guidelines (1977); be 18-65 years old; have a current depressive episode duration of 4 weeks to 2 years; have a minimum Hamilton Depression total score of 18; have at least a moderate rating on the Clinical Global Severity Scale; have acceptable baseline values on vital signs, EKG, physical, and clinical laboratory examinations; and be withdrawn from other psychoactive medication. Patients who had a history or evidence of a seizure disorder, intestinal obstruction, glaucoma, significant cardiovascular disease, or thyroid dysfunction; alcoholism, alcohol abuse, or drug abuse within the past 2 years; or intolerance to amitriptyline were excluded from the study. Patients who were currently suicidal; schizophrenic or schizoaffective; receiving guanethidine or an other agent whose effects are known to be blocked or enhanced by tricyclic antidepressants; or who were pregnant, lactating, or did not agree to employ contraception to avoid pregnancy during the study were also excluded.

Comparison of the bupropion and amitriptyline groups with respect to demographic characteristics indicated that the majority of the patients were females (70% and 62%, respectively), and caucasian (94% and 98%). The average age was 39.7 years for the bupropion group and 36.0 years for the amitriptyline group. Of the 98 patients included in the efficacy analyses, the majority were diagnosed as either manic-depressive, depressed (70%), or with depressive neurosis (23%) according to the Diagnostic and Statistical Manual-II (American Psychiatric Association, 1968). None of the patients had received prior hospitalization for a depressive episode, and the mean duration for the current episode of depression was 6.0 and 7.2 months for the bupropion and amitriptyline patients, respectively.

The efficacy of bupropion was compared to amitriptyline using the Clinical Global Severity of Illness and Improvement Scales (Figure 2), and the Hamilton Depression and Anxiety Scales (Figure 3). Both bupropion and amitriptyline patients showed a significant ($p < 0.05$) improvement from baseline in their severity of illness and Hamilton Depression scores starting on Day 7 of active drug treatment (Study Day 14). Significant improvement from baseline in the Hamilton Anxiety scores occurred starting on Day 14 of bupropion treatment and Day 7 of amitriptyline treatment. For both treatment groups, all subsequent assessments on each scale differed significantly from baseline. Similar equivalency of results were obtained with the Zung Self-Rating Depression and Anxiety Scales. Except for Treatment Day 7 (Study Day 14) on the Hamilton Depression Scale, there were no significant differences in efficacy at any of the nine assessment points for each rating scale between the bupropion and amitriptyline groups. At termination of treatment, 85% of the bupropion and 81% of the amitriptyline patients were rated much or very much improved on the Clinical Global Improvement Scale.

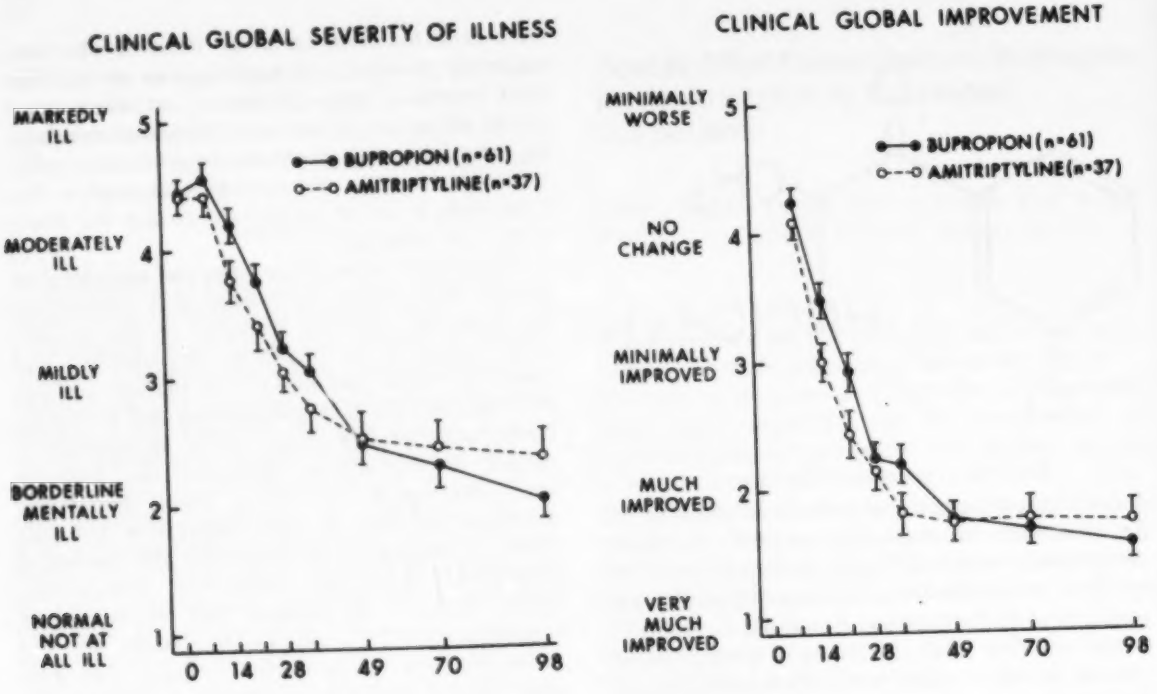

FIGURE 2. Comparison of bupropion vs. amitriptyline on the Clinical Global Severity of Illness and Improvement Scales. (Improvement is judged relative to baseline.)

With respect to safety, bupropion treatment was associated with fewer drug-related side effects than amitriptyline treatment. Side effects were recorded at each assessment day using a modified Treatment Emergent Symptom Scale format (Guy, 1976). Two of the 81 bupropion patients were discontinued due to adverse events (rash) as was one of the 42 amitriptyline patients (disturbed concentration, confusion, and agitation). During treatment, there were five adverse experiences whose relative frequencies, both in terms of percent patient and report incidence, were differentially associated with either amitriptyline or bupropion. Blurred vision, dry mouth, dizziness, and nightmares occurred more often in amitriptyline patients (in 11-27% more patients); whereas, only decreased appetite occurred more frequently in bupropion patients (in 15% more patients). During the posttreatment week, no withdrawal effects were noted in either group. Analyses of mean change in body weights between baseline and termination of treatment showed a mild weight loss (2.1 pounds) by bupropion patients in contrast to a mild weight gain (2.4 pounds) by amitriptyline patients. With respect to vital signs, bupropion treatment resulted in no clinically significant cardiovascular changes, whereas amitriptyline produced significant ($p < 0.05$) increases in supine and standing pulse rates (5 and 6 beats/min, respectively), and a number of reports of orthostatic hypotension.

In conclusion, during a six-center, double-blind outpatient investigation, bupropion (300-450 mg/d) produced antidepressant activity comparable to amitriptyline (75-150 mg/d) with both groups showing significant improvements in their depression scores after 7 days of treatment. Bupropion treatment was associated with fewer drug-related side effects, particularly fewer sedative, anticholinergic, and cardiovascular-related adverse events than those observed with amitriptyline.

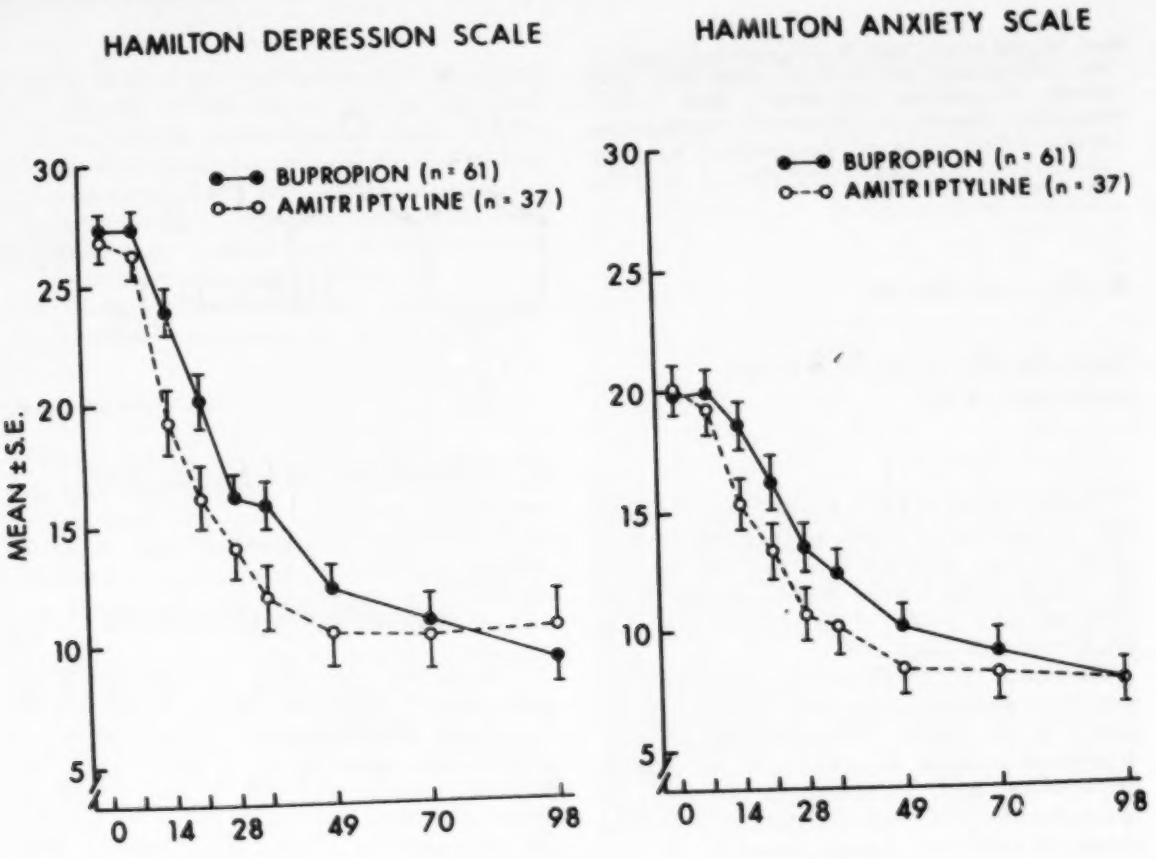

FIGURE 3. Comparison of bupropion vs. amitriptyline on the Hamilton Depression and Anxiety Scales.

Acknowledgment: Investigators contributing data to this multicenter evaluation of the efficacy and safety of bupropion versus amitriptyline included: R.A. Remick, M.D., Vancouver, British Columbia; A.J. Cooper, M.D., Sarnia, Ontario; J. Mendels, M.D., Philadelphia, Pennsylvania; A.N. Singh, M.D., and B. Saxena, Ph.D., Hamilton, Ontario; M.M. Amin, M.D., Pointe Claire, Quebec; and G. Chouinard, M.D., Montreal, Quebec.

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Wellbatrin Studies

Baron Shopsin, M.D.,[1] and Gregor Laakmann, M.D.[2]

Among the 30 or more newer "second generation" antidepressant molecules reviewed by us in recent years, bupropion is one of the few discovered in the United States and one of the more unique in profile of clinical activity (Shopsin, Cassano, & Conti, 1981).

Bupropion HCl (Wellbatrin) is an antidepressant of the propiophenone class, with a structure shown in the Figure. Demonstrating an antidepressant potential in animals in the learned helplessness and tetrabenazine models, its neurochemical profile remains distinct from other standard/marketed antidepressants of the tricyclic-monoamine oxidase (MAO) inhibitor classes. Included in the pharmacological profile of bupropion is an absence of anticholinergic, antihistaminergic, and antiserotonergic properties. At the time of writing, its central chemical mode of antidepressant action awaits clarification (Maxwell, Mehta, Tucker, et al. 1981; Stern, Harto-Truax, Rogers, & Miller, 1981).

This paper is an abstract of data presented at the 1981 NCDEU meeting which focused on three separate studies: a single-blind comparison of Wellbatrin vs. imipramine in depressed outpatients; long-term maintenance or prophylactic effects in both unipolar as well as bipolar manic-depressives; and neuroendocrine studies carried out to help clarify its potential mechanism of action.

[1]New York University School of Medicine, New York, NY 10016, [2]Psychiatrische Klinik und Poliklinik, Universität München, West Germany.

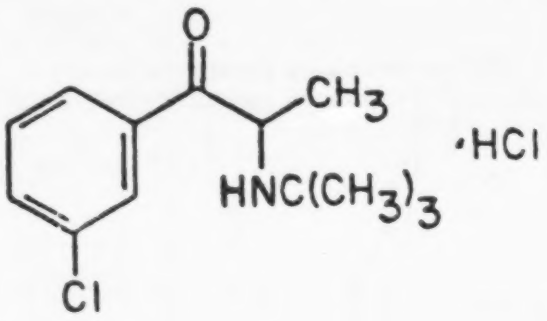

FIGURE. Bupropion HCl (Wellbatrin™)

Wellbatrin-Imipramine Study

The efficacy and safety of three Wellbatrin regimens (150 mg/d, 300-450 mg/d, and 300-900 mg/d) and one imipramine regimen (up to 300 mg/d) were compared in a single-blind, randomized, parallel trial with 40 depressed outpatients. The study was carried out at the Affective Disorder-Lithium Clinic, NYU-Bellevue Hospital Center under conditions of written informed consent. The number of patients examined was limited (10 patients in each drug group), so that conclusions from a biometric standpoint must be circumspect. Within these methodological constraints, it may be concluded that:

1) Both high-dose Wellbatrin and imipramine showed a comparable and statistically significant antidepressant action in endogenously depressed outpatients. These findings were documented using a battery of standard National Institute of Mental Health-Pharmacologic and Somatic Treatments Research Branch (NIMH-PST) objective rating devices including patient self-rating scales. Most patients in the low and mid-dose range groups required switching to high dose medication (i.e., 300-900 mg/d range) after 2 weeks.
2) The speed/onset of action was similar for both compounds and reached statistical significance by the end of the second week.

3) Wellbatrin was well tolerated. There were virtually no side effects recorded for these drug groups irrespective of dosage. There were no anticholinergic side effects; the drug was nonsoporific and did not cause fatigue or drowsiness. Imipromine was accompanied by a high incidence of anticholinergic and central nervous system effects.
4) Vital signs and laboratory tests remained essentially unchanged for both drugs.

Prophylactic Trials

Those patients responding to Wellbatrin, who also had a documented history of illness recurrence at least once yearly during the 2 years immediately prior to Wellbatrin treatment, were continued in an open trial for 1 year. All unipolar and bipolar patients remaining on medication showed no illness relapse and were able to sustain a reduction in dosage and an absence of any side effects (Shopsin, Cassano, & Conti, 1981).

None of the unipolar or bipolar patients showed a swing to mania and none needed the addition of lithium carbonate to prevent or stabilize any such behavioral toxicity.

Three bipolar patients who had never before responded to antidepressant drugs without a swing into a manic state, also did well for a 1-year period on Wellbatrin alone. All three cases were known to us in the clinic for many years. Prior psychoactive treatment responses of these patients were either poor or unsustained, and lithium was unable to prevent or satisfactorily attenuate continued recurrences of high or low mood states. This, then, was the first occasion that any of the three bipolar patients showed any prophylactic response for a 1-year period. There were no attendant side effects.

All patients, unipolar as well as bipolar, relapsed into depression (all unipolar and two bipolar) or mania (one bipolar) within 6 months of discontinuing Wellbatrin; all patients were placed on other medication when Wellbatrin was discontinued because of their history of recurrences, except for the bipolar patient who became manic.

Neuroendocrine Studies

The effect of bupropion on the secretion of growth hormone (GH) and prolactin (PRL) was studied in six healthy male subjects and another six male hyperprolactinemic patients, using a randomized double-blind paradigm. The collaborative study was carried out in Germany at the Outpatient Pscyhiatric Clinic, University of Munich. The six "normal" subjects and six psychiatric patients each received placebo (one dose) and 200 mg bupropion (one oral dose) under conditions of written informed consent. The patient group was pretreated with a neuroleptic drug, haloperidol. The studies with both healthy volunteers and psychiatric patients occurred at an interval of 1 week. After administration of the test substances (i.e., either placebo or bupropion), blood was drawn to measure GH or PRL up to 240 minutes (i.e., 4 hours) thereafter. The data presented clearly indicate that bupropion, in the dose administered, leads to no change in the secretion of GH or PRL in humans. The findings hold both in the normal volunteers and with psychiatric patients pretreated with haloperidol (i.e., rendered hyperprolactinemic). There was no change in the thyroid-releasing hormone (TRH)-induced stimulation of PRL in either the normal volunteers or psychiatric patients (Laakmann, Hoffmann, & Hofschuster, in press).

Conclusion

The present single-blind study data support open trails and double-blind comparisons to the effect that Wellbatrin is an effective antidepressant drug whose clinical response in psychiatric patients is not accompanied by anticholinergic or CNS effects. (Stern, Harto-Truax, Rogers, & Miller, in press). It appears particularly suited for patients with psychomotor retardation. Preliminary data in both unipolar as well as bipolar patients suggest a prophylactic effect for bupropion against acute recurrences of either mania or depression. Finally, in efforts to clarify its potential mechanism of action, we carried out neuroendocrine studies to examine the potential effects of bupropion on central noradrenergic and dopaminergic mechanisms. Our negative findings fail to enhance our understanding of the possible mechanism of action of this new and exciting antidepressant drug.

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Atypical Depressives: A Prelminary Report of Antidepressant Response and Sleep Patterns

Frederic M. Quitkin, M.D.,[1] David Schwartz, Ph.D.,[1] Michael R. Liebowitz, M.D.,[1] Jonathan R. Stewart, M.D.,[1] Patrick J. McGrath, M.D.,[1] Frieda Halpern, M.A.,[1] Joaquim Puig-Antich, M.D.,[1] Elaine Tricamo, R.N.,[1] Edward J. Sachar, M.D.,[1] and Donald F. Klein, M.D.[1]

Although tricyclic treatment for severe depressive disorder was adopted as a standard by 1970, there was still no agreement on the best method of treating the large number of mildy or moderately depressed patients seen in outpatient settings.

In an effort to render antidepressant drug treatment more uniformly effective, investigators began to reconsider two aspects of the problem: refinement of diagnostic classification and alternative treatment strategies. Accumulating evidence now suggests that meaningful subtypes may differentially respond to alternative treatment. It was in this context that we have formulated the present investigation.

[1]New York State Psychiatric Institute, New York, NY 10032.

Subtypes of Depressive Disorder

It has been recognized that some depressed patients, especially among outpatients and those failing to respond to standard tricyclic treatment, show symptoms opposite to the traditional endogenous constellation. These nonendogenous symptoms include overeating and weight gain, initial insomnia without intermittent or early morning awakenings, and mood worsening in the evening. In addition, such patients are responsive to their social surroundings and can be temporarily cheered, although their dysphoric mood returns. This symptomatic picture is referred to as atypical depression (Klein, Gittelman-Klein, Quitkin, & Rifkin, 1980). We wished to test the hypothesis that atypical depressives are more likely to respond to monoamine oxidase inhibitors (MAOI) than tricyclic antidepressants.

Sleep polysomnography has been demonstrated to be altered in some depressive subgroups (Kupfer & Foster, 1978). To further understand the atypical syndrome, sleep studies of this patient group were initiated. All of this work is in the preliminary phase. Data from a treatment study and sleep polysomnography are presented.

Method

This is a 7-week drug study of atypical depressives comparing placebo, a tricyclic antidepressant (imipramine), and a MAO inhibitor (phenelzine). All patients received placebo single-blind for 10 days. Patients who were much improved during the initial placebo phase were removed from the study. Treatment and evaluation of progress after the initial placebo phase was done in a double-blind manner.

Subjects

To be eligible, subjects must meet the Research Diagnostic Criteria for major, minor, or intermittent depression (Spitzer, Endicott, & Robins, 1978). To be diagnosed as having an atypical depressive disorder, subjects must have the essential feature of reactivity of mood. They must also be rated as moderate to severe for at least two of four associated features, which include hypersomnia, overeating, fatigue and lethargy, and rejec-

tion sensitivity. Subjects are excluded if they meet Research Diagnostic Criteria for schizophrenia, schizoaffective disorder, unspecified functional psychoses, or criteria for endogenomorphic depression (Klein et al., 1980). Patients are excluded if they have been treated in the current episode with tricyclics (greater than 150 mg of imipramine/d or its equivalent) or MAOI (45 mg/d or more of phenelzine or its equivalent).

Medication

Each patient receives two bottles of medication. One bottle contains 15 mg phenelzine or matching placebo, and the other contains 50 mg imipramine or matching placebo. The patient will take the phenelzine or its matching placebo in the morning and the imipramine or its matching placebo at bedtime In no case will the patient receive both active medications. Thus, the dosage schedule is fixed up to 4 tablets/day of each medicine or its placebo. This schedule will be delayed, stopped,or reversed in the event of adverse reactions. The patients who have had a complete remission of symptoms will not have their dose increased beyond 4 tablets/day of each medicine or its placebo. However, for patients who have not responded, every attempt will be made to increase the dose to five or six pills of each medication (that is 75-90 mg phenelzine or 250-300 mg imipramine for patients on an active medication).

Results

This is a preliminary report of an ongoing study. To date, 44 patients have been entered into the study. During the initial 10-day single-blind placebo period, 6 were judged significantly improved and removed from the study; 12 patients were randomized to imipramine, 2 were judged significantly improved, 9 were unimproved, and 1 patient dropped out. Twelve patients were randomized to phenelzine, 7 were judged significantly improved, 3 were judged unimproved, and 2 patients dropped out. Thirteen patients were randomized to placebo, 3 were judged significantly improved, and 10 were judged not improved. This data is summarized in the Table.

Table

Preliminary Results: Randomization Phase

	Phenelzine	Imipramine	Placebo	Chi-Square
Improved	7	2	3	7.54*
Unimproved	3	9	10	

*Significant at .05 level.

Sleep Indexes of Atypical Depressives: A Preliminary Examination

Recent work suggests that the EEG sleep indexes of primary depressives differentiate them from other patients as well as normal controls.

Also reported is a preliminary examination of a pilot study of 10 nonbipolar, atypical depressives studied in our sleep laboratory. Data from Williams, Karacan, and Hursch (1974) as well as that from Kupfer, Foster, Coble, McPartland, and Ulrich (1978) were used to serve as a standard for comparing the sleep indexes of the atypical depressive. The use of data recorded in other laboratories for this purpose is viewed as a methodological shortcoming to be corrected in future studies.

The mean age of the 10 patients with atypical depression is 30.6. Their REMP latency on Night 1 is 69.61 min, SD 31.07; on Night 2, 53.05 min, SD 21.96; and on Night 3, 57.87 min, SD 39.60. Williams et al. (1974) reported normative data in the 30-40 age group, where the REMP latency is 82 minutes, SD 24.77. Kupfer et al. (1978) reported that the REMP latency for 47 patients (mean age 45.7 ± 1.9) with primary depression was 39.6, SEM 3.2 and for 47 patients with secondary depression (mean age 45.7 ± 1.9) it was 72.3, SEM 4.3. This would suggest that patients with atypical depression are different from "normals" and that their REMP latency may differentiate them from secondary as well as primary endogenous depressives.

We also examined other sleep measures in this study of atypical depressives. Total sleep time for atypical depressives was close to 400 min (range is 395-406 min on three nights). This is similar to Williams' et al. normals of 423 min and appears to be different from Kupfer's findings of approximately 304 to 336 min in primary and secondary depressives, respectively.

Summary and Conclusions

These preliminary results support the hypothesis that patients referred to as atypical depressives have a greater likelihood of responding to MAOI than to TCA or placebo. If this preliminary trend persists, it would have important clinical and heuristic implications.

It would suggest that MAOI is the treatment of choice for this patient group. Differential responsivity of MAOI supports the validity of the phenomenologic depressive subtype and suggests that the pathophysiology of this patient subgroup differs from endogenous depressives. It would also be relevant to determine if this response of atypical depressives is specific for hydrazine derivatives such as phenelzine, or whether it also occurs with nonhydrazine derivatives such as tranylcypromine, or specific MAOI such as deprenyl or clorgyline.

The shortened REM latency of atypical depressives suggests that they do share some of the characteristics of other depressive disorders. It might be concluded that this is a mild form of depressive illness. If that were the case, they should respond to TCA as well as MAOI. Since that does not appear to be the case, we think this may be a form of affective disorder whose treatment response and pathophysiology is distinctly different from patients with endogenous forms of the illness.

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Biological and Clinical Studies of Tardive Dyskinesia

Robert C. Smith, M.D., Ph.D.,[1] Richard Allen, D.P.H.,[1] Jack Gordon, M.D.,[1] Chandra Misra, Ph.D.,[1] Joseph Schoolar, M.D., Ph.D.,[1] Judith Wolff, R.N.,[1] and Beng T. Ho, Ph.D.[1]

A series of surveys, small treatment trials, and biological studies have been conducted on patients with tardive dyskinesia (TD). In all studies, TD was rated using the Smith-TRIMS TD scale which evaluates multiple symptom areas of dyskinetic and extra pyramidal type symptoms.

A prevalence study of TD was done in eight hospitals in the state of Texas using an age-stratified random sampling procedure (about 50% of the sample below and 50% above the age of 50). Most patients with at least minimal symptoms of TD on initial rating were evaluated for more definite dyskinesia with TD ratings on at least two occasions. On a selected sample of patients, a blood sample was drawn to measure plasma neuroleptics, measured by radio-receptor (RR) assay techniques, during an additional TD rating. For the diagnosis of a positive case of TD, a subject had to have a total TD score of at least 5 on the Smith-TRIMS TD scale on two occasions.

Using these rating procedures and criteria, 35.8% of patients in the sample had definite TD, with the rate about twice as high in patients over the age of 50 (47.1% positive cases) as in cases under the age of 50 (22% positive cases). The percent of patients with definite TD increased in a montonic fashion between the ages of 50 and 60 or 70 but did not increase further in the oldest age groups (Figure 1). Females had higher dyskinesia scores than males in the younger and middle age groups, but did not show a consistent trend for higher TD scores in patients above 60 or 70 years of age.

[1]Sections of Biological Psychiatry, Neurochemistry and Neuropharmacology, and Biological Psychiatry Research Team, Texas Research Institute of Mental Sciences, Texas Medical Center, Houston, TX 77030.

Note: Address communications to Dr. Smith, Chief, Biological Psychiatry.

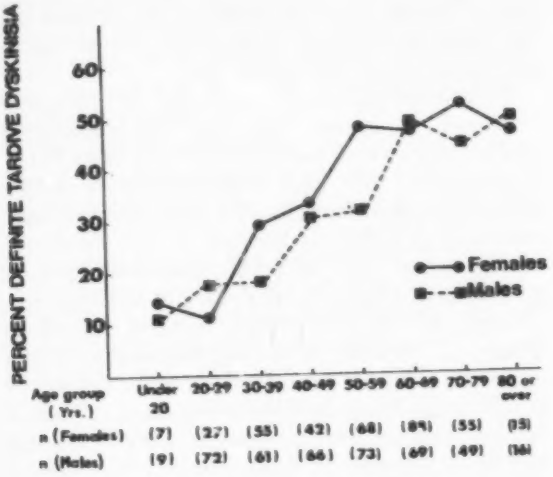

FIGURE 1. Effects of age and sex on the prevalence of tardive dyskinesia

Radio-receptor plasma levels of neuroleptic drugs that the patients were receiving correlated significantly but negatively with TD scores. Patients who met criteria for a positive case of TD had about 40% lower plasma neuroleptic levels than patients without TD (*see* Table). A similar trend was found in patients under the age of 50 than in patients over the age of 50.

In a small sample of patients treated with lecithin (35 gm/d of 53% phosphatidylcholine) in a double-blind crossover design, lecithin did not have consistent or statistically significant effect in ameliorating TD severity scores; one or two patients showed improvement and one or two patients had a worsening of TD symptoms (Figure 2).

Patients with TD had significantly higher plasma pseudocholinesterase levels than controls (Figure 3), but they showed no significant difference in platelet monoamine oxidase compared to schizophrenic controls.

Table

Lower Neuroleptic Plasma Levels in Patients with Definite Tardive Dyskinesia

	Mean Neuroleptic Plasma Level* (RR Assay)		
	Definite TD	No TD	TD Percent Decrease
All Patients	263 ± 35** (101)†	436 ± 98 (52)	−40%
Patients over 50 years	248 ± 42 (65)	450 ± 157 (22)	−45%
Patients 50 years or under	293 ± 65 (36)	430 ± 127 (30)	−32%

* Radio-receptor assay ng/ml chlorpromazine equivalence
**Each number is mean ± s.e.m.
† Number of patients

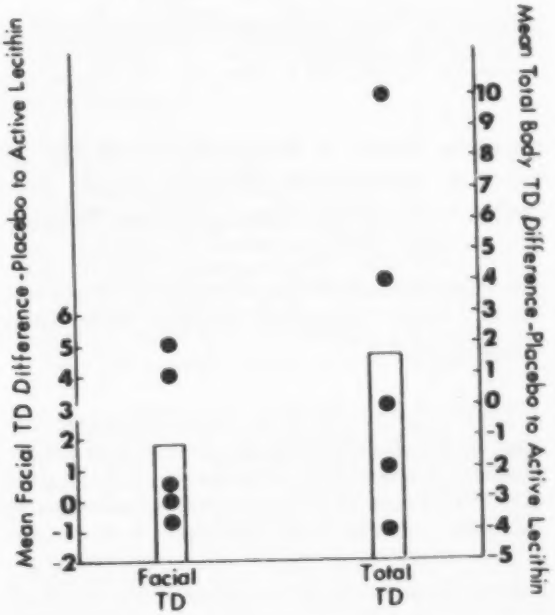

FIGURE 2. Effects of lecithin on tardive dyskinesia. Each point represents the mean difference of placebo minus lecithin scores; a higher score indicates improvement.

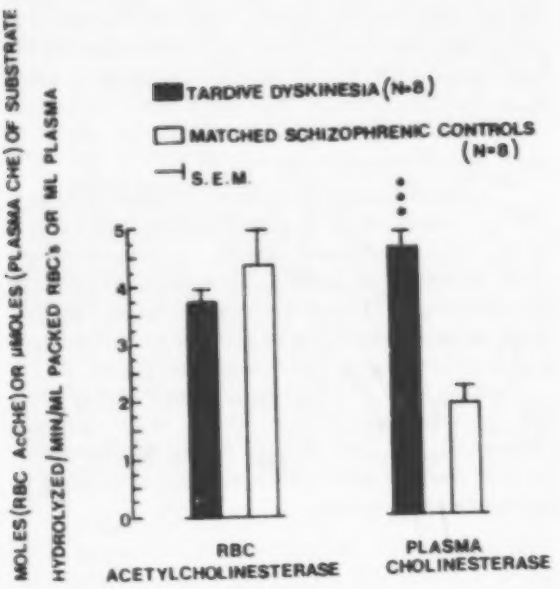

FIGURE 3. Plasma pseudocholinesterase values in patients with TD and control.

Results From a Prospective Study of Tardive Dyskinesia Development: Preliminary Findings Over a 2-Year Period[1]

John M. Kane, M.D.,[2] Margaret Woerner, Ph.D.,[2] Paul Weinhold, Ph.D.,[2] and James Wegner, M.A.[2]

Tardive dyskinesia (TD) remains a major concern in the pharmacological treatment of schizophrenia (American Psychiatric Association, 1979). The lack of a proven, safe, and effective treatment for TD makes attempts at prevention urgent. A review by Kane and Smith (1981) revealed prevalence rates ranging from 0.5% to 56% (mean = 20.1%) among 56 neuroleptic-treated samples. Among untreated samples, the prevalence of abnormal movements ranged from 0 to 36.7% (mean = 5.1%). Since these samples may have differed on many variables other than neuroleptic exposure, contrasting them is not ideal. Despite this, the epidemiological data implicating neuroleptic treatment as a major etiological factor are compelling.

Even with the enormous range in prevalence estimates, it seems clear that the majority of neuroleptic-treated patients do not develop TD. It is important, therefore, to identify factors which might increase vulnerability and then develop strategies to minimize the risk.

This report presents preliminary findings from an ongoing prospective study of TD development. To date, 777 psychiatric patients have entered the study; the majority have been followed for 1 to 3 years. Patients are examined every 3 months and rated on the Simpson Dyskinesia Scale, Simpson Angus Scale (for extrapyramidal side effects), and the Brief Psychiatric Rating Scale. Electroencephalograms and psychometric testing are done at baseline, and detailed histories of psychotropic medications are obtained. Ratings are made blind to treatment history.

Patients who develop "questionable" signs (defined globally) are seen monthly. Diagnosis of presumptive TD requires ratings of at least mild TD by three raters following separate examinations. TD cases are videotaped, discontinued from antipsychotic drugs if possible, and rated biweekly for at least 3 months.

The demographic characteristics of the first 328 patients who were at risk (neuroleptic-treated) include: mean age = 27 (*SD* 9); 59% male; 59% schizophrenic, 17% affective disorder, 12% schizoaffective on the Diagnostic and Statistical Manual-II (DSM-II). The majority had less than 1 year total cumulative neuroleptic exposure prior to study entry (mean exposure 21 months, median 10 months).

To date, 44 cases of presumptive TD have developed during the study. Their characteristics include: 50% male; mean age = 33 (*SD* 12); mean cumulative neuroleptic exposure 30 months (*SD* 31); 34% schizophrenic; 36% major affective disorder; 20% schizoaffective. These patients were classified according to the Research Diagnoses for Tardive Dyskinesia (RD-TD) (Schooler & Kane, 1981) as follows: 30 persistent TD (18 neuroleptic-free and 12 with concurrent neuroleptics);

[1]This project was supported by USPHS, NIMH Grant MH-32369.

[2]Long Island Jewish-Hillside Medical Center, P.O. Box 38, Glen Oaks, NY 11004.

8 transient TD, 3 probable, and 3 withdrawal TD.

A life-table analysis employing the first 328 at risk subjects indicated a cumulative incidence of TD of 12% (95% confidence interval 6%-18%) at the end of 4 years of total cumulative neuroleptic exposure. Our effective sample size beyond 4 years is still too small to determine incidence beyond this point.

The patients who developed TD had a mean cumulative neuroleptic exposure prior to TD diagnosis of 158 weeks (*SD* 134) compared with 122 weeks (*SD* 122) for those without TD when last examined (two-tailed p value = .12).

Additional analyses of risk factors eliminated those who had shown any "questionable" signs of TD to provide a sharper distinction between those who developed TD and those who remained "clear" up to the most recent observation. In addition, to explore factors which might indicate those most vulnerable to TD development (Kane, Struve, Weinhold, & Woerner, 1980), TD cases were divided into two groups: those developing TD after less than 2 years of neuroleptic exposure (early TD) and those developing TD after more than 2 years (late TD).

The results indicated that TD cases had longer exposure to neuroleptic and antiparkinsonian drugs prior to study entry than did patients without TD. TD cases compared with non-TD patients were older at study entry, had had a longer psychiatric history, and had more often been treated with electroconvulsive therapy (ECT). Early and late TD cases did not differ significantly on these variables. Early TD cases had significantly lower maximum doses of neuroleptics than late TD cases, suggesting that early TD onset is not related to the use of higher doses of medication. The TD group as a whole, however, did receive significantly higher maximum doses than the non-TD group. Late TD cases had had more neuroleptic-free intervals of at least 1 month and were more likely to have taken combined neuroleptics than both the early TD and clear groups. However, the effects of the latter three variables may be mediated by length of neuroleptic treatment with which they are correlated.

Interestingly, the history of extrapyramidal side effects and the number of months of exposure to lithium prior to study entry were significantly related to the "early" onset of TD. The former has been suggested as a risk factor in the literature (Crane, 1972) and will be explored in more detail in subsequent analyses. The lithium finding may reflect a possible increased risk among patients with affective illness (Rosenberg, Niven, & Hanson, 1977; Davis, Berger, & Hollister, 1976) or may involve unknown long-term neurochemical effects of lithium.

The ECT finding also suggests that diagnosis may be a factor. We found no relationship between DSM II-diagnosis and TD development; however, further exploration using Research Diagnostic Criteria (RDC) diagnoses for matched TD and non-TD cases may prove more fruitful.

Other variables showing no relationship to TD development were: sex, psychometric test scores, history of CNS injury or dysfunction, medication at study entry, potency of predominant neuroleptic, total exposure to tricyclic antidepressants, monoamine oxidase inhibitors, minor tranquilizers, and anticonvulsants.

It is important to emphasize the preliminary nature of these findings. Many risk factors are intercorrelated, and a larger number of TD cases will be necessary in order to carry out more meaningful analyses.

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Impairment of Swallowing, Tardive Dyskinesia, and Anticholinergic Drug Use

Thomas J. Craig, M.D., M.P.H.,[1,2] Mary Ann Richardson, M.A.,[1] Nigel M. Bark, M.D.,[1,3] and Roman Klebanov, M.D.[4]

The influence of psychotropic medication on the swallowing mechanism has been a source of controversy since the mid-1950s when case reports of choking deaths among medicated psychiatric patients began to appear (Feldman, 1957; Hollister, 1957; Plachta, 1965; Wardell, 1957). A recent case-control study of choking deaths revealed that patients who choked to death were twice as likely to be receiving two or more drugs with significant anticholinergic effects than matched controls (Craig, 1980). An unpublished report (Moore & Book, 1970) claimed that 40% of an unselected sample of psychiatric patients were found to have an impairment of the gag reflex in contrast to only 9% of "normals." Case studies of two patients with tardive dyskinesia indicated a difficulty in swallowing (Brandon, McClelland, & Protheroe, 1971; Gilbert, 1969.) These findings plus experimental evidence (Bieger, Giles, & Hockman, 1977) implicating dopaminergic mechanisms in the pharyngeal phase of swallowing led to the present study.

Method

The present study was conducted using a nonrandom sample of long-term psychiatric patients in a large state hospital. All but one patient were diagnosed schizophrenic by the treating clinician using Diagnostic and Statistical Manual-II criteria. A research scientist with extensive experience carried out ratings of tardive dyskinesia using the Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976), and the Simpson Abbreviated Rating Scale (ADS) (Simpson, Lee, & Zouback, 1979), and of parkinson-like symptoms using the Neurological Rating Scale (NRS) (Simpson & Angus, 1970). The scoring of the NRS and the ADS were adapted to conform with the AIMS ratings of 0 = absent, 1 = minimal or questionable, 2 = mild, 3 = moderate, and 4 = severe. Separate from this examination but within the same time period, two research psychiatrists independently assessed each patient's gag reflex. The technique and ratings described were developed after a study of the literature and consultation with local experts in neurology and otorhinolaryngology plus a pilot test in patients not included in the study. Interrater agreement for this gag reflex rating was acceptably high (Kappa = 0.76, $Z = 7.05$). After both clinical procedures were completed on all patients, a history of current medication usage was obtained from each patient's clinical chart by the research scientist. Data analysis was carried out using the chi-square statistic (Fleiss, 1973) and the log-linear model technique (Fienberg, 1978).

Results

A total of 56 patients were studied of whom 34 (60.7%) were men, 21 (36.2%) were less than 50 years old, and 43 (76.8%) were continuously hospitalized for more than 10 years. Thirty-three (58.9%) of the patients were rated normal on gag reflex with 8 (14.3%) rated variable, and 15 (26.8%) impaired. Initial analyses were carried out with the three dependent variable groups (Normal, Variable, Impaired). However, since the Variable and Impaired groups were virtually identical in their characteristics, these groups were combined in later analyses. There were no significant differences among the groups on the variables of age, sex, length of stay, extrapyramidal symptoms, or neuroleptic use as measured in chlorpromazine equivalents.

The Table shows the prevalence of gag reflex impairment among patients classified according to both presence or absence of tardive dyskinesia (using the ADS and AIMS) and use of anticholinergic medication. As indicated, the proportion of patients with gag reflex impairment is roughly

[1]Rockland Research Institute, Orangeburg, NY 10962.
[2]Department of Psychiatry, New York University, New York, NY 10016.
[3]Columbia University, New York, NY 10028.
[4]New York Medical College, Valhalla, NY 10595.

Address correspondence to Dr. Craig at 40 Woodbine Road, New City, NY 10956.

similar for patients with one or neither of these conditions, ranging from 12.5-33.3%. In striking contrast, almost three-fourths of those patients with tardive dyskinesia and using anticholinergic drugs showed gag reflex impairment, suggesting an interaction effect among these factors.

Discussion

Due to the highly selective nature of the patient population studied (long-stay schizophrenics exposed to long-term medication use), the generalizability of the present findings to more acute patient populations with heterogeneous drug use and diagnoses requires further replication. However, the prevalence of impaired gag reflex in these patients (41.4%) is remarkably similar to the figure found in the only previous report addressing this issue (Moore & Book, 1970).

The present findings suggest an interrelationship among tardive dyskinesia, the use of anticholinergic drugs, and impairment of the gag reflex. It is generally accepted that the use of anticholinergic agents aggravates the signs of tardive dyskinesia once the latter have been established (Gerlach, Reisby, & Randrup, 1974; Klawans, Goetz, & Perlik, 1980). The association of both these variables with impairment of the gag reflex is not as well defined.

Neurotransmitters involved in the gag reflex arc include glutamic acid (afferent impulses), dopamine (centrally), and nicotinic acetylcholine receptors at the afferent striated muscle motor end plate (DeJong, 1950; Kaelle, 1975). Dopamine has been shown in animal studies to both facilitate and inhibit swallowing under varying circumstances (Bieger, Giles, & Hockman, 1977). Thus, one possible explanation for the observed association among these three variables could be the hypothesis that the mechanism of impairment of the gag reflex is analogous to that of tardive dyskinesia, being a supersensitivity phenomenon related to prolonged block of dopamine receptors. The fact that the reflex is inhibited rather than exaggerated, which is the case in tardive dyskinesia, could suggest that there is a relative predominance in supersensitivity of inhibitory dopamine receptors over facilitating receptors which might be further enhanced by a central hypocholinergic effect induced by anticholinergic drugs. This hypothesis would be consistent with recent

Table

Tardive Dyskinesia, Anticholinergic Drug Use, and Pharyngeal Reflex

	Pharyngeal Reflex: Normal		Variable/ Impaired		
	No	%	No	%	Chi-square
Simpson ADS Global					
None/Questionable:					.01 NS
No Anticholinergic Drugs ($N = 9$)	7	77.8	2	22.2	
Anticholinergic Drugs ($N = 8$)	7	87.5	1	12.5	
Mild-Severe:					5.80*
No Anticholinergic Drugs ($N = 20$)	14	70.0	6	30.0	
Anticholinergic Drugs ($N = 19$)	5	26.3	14	73.7	
AIMS Global Severity					
None/Minimal:					.18 NS
No Anticholinergic Drugs ($N = 6$)	4	66.6	2	33.3	
Anticholinergic Drugs ($N = 4$)	3	75.0	1	25.0	
Mild-Severe:					4.33†
No Anticholinergic Drugs ($N = 23$)	17	73.9	6	26.1	
Anticholinergic Drugs ($N = 23$)	9	39.0	14	61.0	

*Significant at .02 level.
†Significant at .05 level.

evidence showing the existence of both inhibitory and facilitating dopamine receptors in various parts of the brain (Klawans et al., 1980).

Alternative hypotheses invoking a primary role for anticholinergic drugs in this mechanism seem less likely, in view of their relatively weak and inconsistent impact on the swallowing mechanism (Bieger et al., 1977), and the fact that they exert their influence only on muscarinic acetylcholine receptors, and thus should have no influence on the nicotinic receptors at the motor endplate (Richelson & Divinetz-Romero, 1977). The present data suggesting an interaction between tardive dyskinesia and anticholinergic drug use support this conclusion.

Whatever the underlying mechanism, the present study strongly suggests that patients with tardive dyskinesia receiving anticholinergic drugs are at extremely high risk of also having an impaired gag reflex. This finding reinforces the recommendation that anticholinergic agents be avoided in the treatment of patients with tardive dyskinesia although, as has been noted (Klawans et al., 1980), tardive dyskinesia and extrapyramidal symptoms can coexist and thus pose a therapeutic dilemma. It remains for further study to determine whether the discontinuation of these agents might result in a restoration of the gag reflex.

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Lecithin Treatment of Tardive Dyskinesia—A Progress Report

Brian G. Anderson, M.B., Ch.B.,[1] Dean Reker, R.N.,[1] Miodrag Ristich, M.D.,[1] Eitan Friedman, Ph.D.,[2] Miriam Banay-Schwartz, Ph.D.,[3] and Jan Volavka, M.D., Ph.D.[1]

Tardive dyskinesia (TD) is thought to be related to an imbalance between the dopaminergic and cholinergic systems in the striatum (1). It is believed that there may be a relative deficiency of acetylcholine (Ach) neurotransmission in this area. Some studies have reported beneficial effects in TD using Ach precursors or agonists such as choline, lecithin or physostigmine (2,3,5,6). Lecithin contains phosphatidylcholine (PC) which is metabolized to choline. Oral administration of lecithin elevates plasma choline levels (7) and may increase brain choline and Ach levels (4). Different commercial lecithins contain varying concentrations of PC and impurities, e.g., fatty acids and phosphatidylethanolamine. The authors report progress in a study attempting to replicate beneficial effects of lecithin in TD.

Method

Subjects

Nine female inpatients who gave informed consent served as subjects. Prerequisites to enter the study were: 1) a history of neuroleptic treatment and 2) moderate to severe TD on the Abnormal Involuntary Movement Scale (AIMS) as judged independently by two experienced raters. Age range was 32-77 years (mean 62 yrs), diagnosis by Diagnostic and Statistical Manual-III (DSM-III) criteria was chronic schizophrenia, and three patients also had mild dementia. Duration of neuroleptic treatment was 2-21 years (mean 6 yrs); patients receiving neuroleptics at the beginning of the study had been on the same dosage for 4-12 months (mean 6 mos) and were maintained on this dosage throughout the study. Three patients had been on no medication for 6, 7, and 24 months. TD was assessed using AIMS for 2-8 months before entering the study. The state of dentition was as follows: two subjects were edentulous, four were pre-edentulous (i.e., only 1 or 2 teeth present), and three had poor dentition (i.e., 4-26 teeth missing).

[1]New York University at Manhattan Psychiatric Center, Ward's Island, NY 10035.
[2]New York University, New York, NY 10028.
[3]Center for Neurochemistry, Rockland Research Institute, Ward's Island, NY 10035.

Correspondence should be addressed to Dr. Anderson.

Procedure

This is a crossover, placebo-controlled, double-blind study. The treatment and placebo periods lasted 4 weeks with pretreatment, washout, and posttreatment periods of 2,4, and 2 weeks, respectively. Lecithin or placebo was given in a milk shake at 8 a.m. and 4 p.m. TD was assessed weekly at the same time of day using AIMS, by two blind raters who had an interrater correlation coefficient of 0.93; videotapes of the examinations and polygraph recordings of facial movements were also taken. Weekly plasma choline levels were assayed, using the Jendin–Handin gas liquid chromatography (GLC) method, from blood samples drawn before the 8 a.m. dose. Other parameters measured weekly were the Brief Psychiatric Rating Scale, the Hamilton Depression Rating Scale, and weight.

Results

The first trial involving seven subjects and using Phospholipon-100 (American Lecithin Co., soyabean extract) at a dose of 31.5 gm/70 kg/d showed no change in TD ratings in the presence of consistently elevated plasma choline levels while taking lecithin (Table). Phospholipon-100 was initially chosen because it has one of the highest concentrations (93.5%) of PC. There were no side effects. An attempt was then made to replicate the findings of Jackson, Nuttall, Ibe, and Perez-Cruet (1979), who reported improvement in TD using Type IXE lecithin (Sigma Chemicals, egg-yolk extract) which has 54% PC. The dosage of 50 gms/70 kg/d used by Jackson et al. (1979) was given to five subjects in the present study for 3

weeks. Again, no improvement in TD was noted in the presence of consistently elevated plasma choline levels while receiving lecithin (Table). Because there were no adverse side effects from Phospholipon-100, a trial has been completed in three subjects using a higher dose of this lecithin, i.e., 50 gm/70 kg/d. These subjects all showed a reduction in AIMS scores during the second week of treatment, but this was not sustained throughout the 4-week treatment period (Table).

Table

AIMS Scores* and Plasma Choline Levels†

	Baseline 2 Wks Mean	Lecithin Treatment (Wks) 1	2	3	4	Placebo 4 Wks Mean
		Phospholipon-100 31.5 gm/70 kg/d				
AIMS ($N = 7$)	15.6	15.8	16.6	16.8	16.4	15.7
Plasma Choline ($N = 5$)	6.0	20.4	18.6	20.7	-	-
		Sigma IXE 50 gm/70 kg/d				
AIMS ($N = 5$)	17.8	16.8	18.2	17.6	-	19.3
Plasma Choline ($N = 2$)	8.6	20.9	27.8	31.6	-	8.6
		Phospholipon-100 50 gm/70 kg/d				
AIMS ($N = 3$)	15.5	15.8	11.0	12.6	14.8	15.5
Plasma Choline ($N = 3$)	8.4	32.9	33.3	-	28.8	-

*AIMS scores are the sums of items 1-7 on the AIMS scale and are shown as the average for N, the no. of subjects.

†Plasma choline levels are in n moles/ml. and are the averages for N subjects.

Discussion

The investigators were unable to show improvement in TD using two different lecithins. The patient group described here is similar to that of Jackson et al. in terms of diagnosis, age, and sex. However, there may be various subtypes of TD which are biochemically different but clinically indistinguishable from each other; such differences in patient selection may account for the failure to replicate Jackson's results. Furthermore, it is possible that patients vary in their permeability of the blood-brain barrier for choline and, therefore, raising plasma choline may have quite different effects on choline levels in the brain in different patients. Finally, the number of patients in the reported study, as well as in other reports, is still far too small for a conclusive statement; the investigators are studying additional patients.

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Effects of AMPT on Tardive Dyskinesia and Psychosis

Henry A. Nasrallah, M.D.,[1] Robert E. Smith, M.D.,[1] Frederick J. Dunner, M.D.,[1] and Mona McCalley-Whitters, B.S.N.,[1]

Dopamine (DA) receptor supersensitivity in the striatum after chronic neuroleptic intake is believed to be the basic pathophysiology of tardive dyskinesia (Klawans, 1973). In addition, DA receptor supersensitivity in the mesolimbic and mesocortical tracts has been suggested as possibly associated with psychosis (Davis & Rosenberg, 1979). DA antagonists such as receptor blockers (neuroleptics), stores depletors (reserpine), and synthesis inhibitors (alpha methyl paratyrosine) (AMPT) are known to mask tardive dyskinesia (Baldessarini & Tarsy, 1978).

AMPT has been shown to potentiate the antipsychotic effect of neuroleptics (Carlsson, Persson, Roos, & Walinder, 1972) but not in neuroleptic-resistant schizophrenic patients (Nasrallah, Donnelly, Bigelow,et al. 1977). AMPT has also been reported to improve the symptoms of tardive dyskinesia in about 50% of patients receiving 4 g/day for 3 days (Gerlach, Reisby, & Randrup, 1974; Gerlach & Thorsen, 1976).

In this study, the effects of AMPT on tardive dyskinesia and psychosis are described.

Method

Six patients with chronic schizophrenia or schizoaffective psychosis and persistent tardive dyskinesia of over 2 years' duration, consented to participate in the study. Their ages ranged from 26 to 71 years. Three patients were drug-free at the time of the study, while three others were receiving maintenance neuroleptic medication. Identical capsules of AMPT and placebo were given in a double-blind, crossover (placebo-active-placebo) design. Depending on body weight, patients received 1.5 to 3.0 g/d of AMPT for 4 weeks, with 2-3 weeks of placebo before and after. Weekly videotapes of the Abnormal Involuntary Movement Scale (AIMS) were randomized and rated blindly by two psychiatrists. Psychosis was rated weekly using the Brief Psychiatric Rating Scale (BPRS).

Results

The results are summarized on the Table. Five out of six patients had a reduction in their tardive dyskinesia AIMS scores after 2 weeks of AMPT. However, after 2 more weeks of treatment with AMPT, four patients showed worsening of tardive dyskinesia while two patients had sustained improvement.

As for the psychosis ratings, after 2 weeks of AMPT treatment the BPRS scores improved for one patient, worsened for two others, and were essentially unchanged for three patients. After 4 weeks of AMPT treatment, all three patients who were receiving maintenance neuroleptic medication showed improvement in the BPRS scores, while all three neuroleptic-free patients showed worsening of their psychosis ratings.

Discussion

The data suggest that AMPT improves tardive dyskinesia initially, probably by inhibiting DA synthesis and decreasing the availability of DA to supersensitive postsynaptic DA receptors. However, continued treatment with AMPT appears to cause a rebound increase in postsynaptic DA receptor supersensitivity (Nasrallah et al., 1977) associated with a reappearance of the dyskinetic symptoms. This suggests that AMPT may not be useful in the long-term treatment of tardive dyskinesia, and that inhibition of DA synthesis probably would not correct the underlying pathophysiology of tardive dyskinesia.

The effect of AMPT on psychosis in this study suggests that AMPT, given alone, may exacerbate psychosis, but if the patient is already on a regimen of antipsychotic medication, then the addition of AMPT seems to produce further improvement in psychosis ratings.

It is possible to postulate that prolonged treatment with AMPT alone in schizophrenic patients may induce DA receptor supersensitivity in both the nigrostriatal as well as mesolimbic DA tracts, which would clinically manifest as tardive dyskinesia and psychotic relapse, respectively.

[1]VA Medical Center and Department of Psychiatry, University of Iowa College of Medicine, Iowa City, IA 52240.

Table

Effects of AMPT On Tardive Dyskinesia (AIMS Scores) and Psychosis (BPRS Scores)

	Total AIMS Score				Total BPRS Score			
Patient No.	Placebo	AMPT (2 Weeks)	AMPT (4 Weeks)	Placebo	Placebo	AMPT (2 Weeks)	AMPT (4 Weeks)	Placebo
1*	12	8	10	9	19	17	42	27
2	10.5	5.5	10.5	14.5	25	23	18	23
3*	10	11	12.5	12.5	15	22	35	16
4*	17	14.5	8	21	24	28	36	34
5	5.5	1	0	2	12	12	9	2
6	7	2	3.5	3.5	20	8	7	8

*Patients who were neuroleptic-free prior to and during the AMPT trial.

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Receptor Sensitivity Modification in the Treatment of Tardive Dyskinesia[1]

Murray Alpert, Ph.D.,[2] Florence Diamond, M.S.,[2] and Arnold J. Friedhoff, M.D.[2]

Increase in dopamine receptor sensitivity is widely thought to underlie tardive dyskinesia (TD) (American Psychiatric Association, 1979). The increased sensitivity is postulated to be a compensatory reaction to the decreased access of dopamine to the postsynaptic receptors through the blocking action of neuroleptic drugs. This study explores a novel treatment approach to TD (Friedhoff & Alpert, 1978); testing the hypothesis that dopamine sensitivity can be down-regulated by temporarily increasing dopamine levels. To accomplish this, increasing doses of L-DOPA are gradually administered, waiting at each dose increment for evidence of adaptation. Following adaptation to a 1-month course of treatment at the target dose, the L-DOPA is discontinued. It is expected that improvement will persist if normal receptor sensitivity is reestablished, and transmitter levels are permitted to return to their usual levels.

Method

Subjects

Subjects were patients in state hospitals who met the following inclusion criteria: 1) a history of at least 2-years' neuroleptic medication; 2) no evidence of abnormal movements prior to receiving neuroleptic drugs; and 3) at least three ratings of mild or one rating of moderate severity of movements on Items 2 (lips), 3 (jaw), and 4 (tongue) of the Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976). Initially only drug-free patients were included, but the study was extended to include patients requiring maintenance neuroleptics. Patients were followed for a period of at least 6 weeks prior to baseline during which they remained drug free or their neuroleptic medication remained unchanged. Anticholinergic drugs were not permitted. Inclusion Item 3 had to

[1]This study was supported by USPHS Grants MH-28892, MH-08618, and Research Scientist Award MH-14024 to A.J.F.

[2]Department of Psychiatry, New York University Medical Center, New York, NY 10016.

be satisfied at the baseline rating just prior to initiation of L-DOPA treatment.

Procedure

Patients were randomly assigned by a nonblind medicating psychiatrist to one of three target doses of carbidopa/L-DOPA as Sinemet: 30/300 mg/d, 50/500 mg/d, and 75/750 mg/d, which was administered orally in divided doses with meals. There was a dose-finding period of 4 weeks during which the dosage was increased as frequently as once a week, and the target dose was maintained for an additional 4 weeks. Increments in dosage were skipped and the dose-finding phase extended if the patient showed evidence of hypotension or significant activation of movement or behavior. In some cases, the target dose was continued to synchronize with the blind evaluators, visit. Patients were treated for an average of 72 days with a range of 56-126 days and received between 11.8 and 54 g of L-DOPA. Six patients received less than 21.9 g and nine patients received more than 33.9 g. These two groups will be reported as low-dose and high-dose groups.

The AIMS was administered as recommended by the Psychopharmacology Research Branch* of the National Institute of Mental Health (NIMH) (Guy, 1976) at baseline, weekly during L-DOPA treatment, and 4 weeks following termination of L-DOPA, which served as an outcome measure. Evaluators were blind as to dose and to where the patient was in the course of treatment. Sedatives were permitted throughout the trial but not within 12 hours of an AIMS rating.

The authors found that summing the AIMS scores is a less satisfactory reflection of pathology, and the data presented here have been derived by squaring the item score before summing. The rationale for squaring and the psychometric properties of the squared scores will be described separately (Alpert, Diamond, & Taleporos, Unpublished data). Intuitively, it may be seen that a patient with three scores of 1 should not be seen as showing equal pathology as a patient showing one score of 3. Squaring the scores, then summing, is a more adequate reflection of pathology.

*Now the Pharmacologic and Somatic Treatments Research Branch

Abnormal Movements of L-Dopa Treated (N=15) and Comparison Group of Equivalent Baseline Pathology (N=10). Second Rating Is Four Months After Baseline.

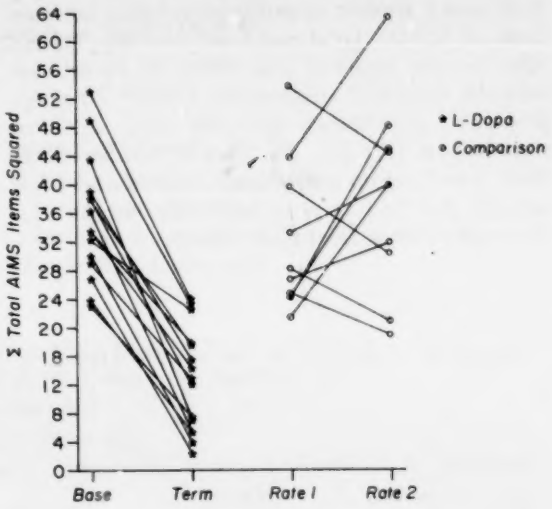

FIGURE 1

Results

Baseline and termination AIMS² Total for 15 patients treated with L-DOPA were compared with 10 patients who met the inclusion criteria but who were not treated with L-DOPA and were evaluated using the AIMS on two occasions approximately 12 weeks apart. The comparison group was matched with the experimental group for age, sex, and baseline AIMS score, but did not receive placebo. (Figure 1). Patients treated with L-DOPA uniformly showed some improvement at termination ratings and for about half the patients the change was clinically significant. Such changes were not apparent in the comparison group. One-way analysis of covariance for AIMS² Total, covarying baseline score, showed a reliable effect for L-DOPA treatment ($F = 25.90$, $p < .001$, df 2,22).

A comparison of low-dose ($N = 6$) and high-dose ($N = 9$) L-DOPA groups at baseline and termination AIMS² Total demonstrated relatively similar slopes, but the high-dose group showed more frequent "good" outcomes (Figure 2). It can

be seen that the six lowest scores at termination were obtained by the high-dose group. Through randomization, the low-dose group may have had slightly higher baseline scores; in a multiple regression analysis examining the effect of dose, there was a modest negative correlation between baseline AIMS[2] Total and dose ($r = -.28$) (Table). After having removed this effect, the correlation between dose and termination AIMS[2] Total approached significance ($p = .08$) and achieved significance ($p = .05$) for Facial[2] scores. Since there was random assignment to dose and blind ratings, this finding provides further support for the suggestion of treatment efficacy.

Comparison of Outcome for Low and High Dose L-Dopa Treatment

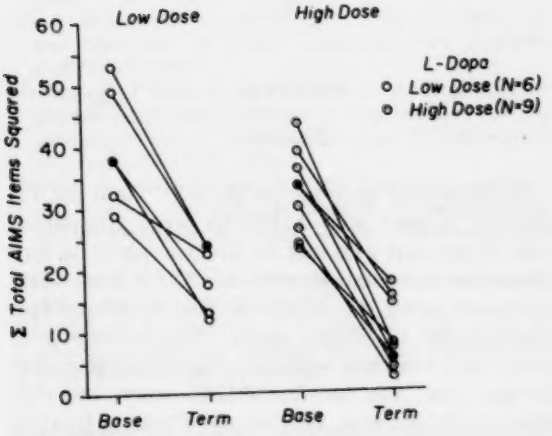

FIGURE 2

Discussion

This report describes a dose ranging study of a novel treatment approach to TD based on the assumption that the TD is related to an underlying pathogenic dopamine receptor supersensitivity, and that this supersensitivity may be reversed if dopamine levels are increased. In these trials it was found that dopamine levels may be safely increased in psychotic dyskinetic patients if incremental steps are carefully controlled. When this is done, there is some evidence that dyskinetic movements may be modestly exacerbated initially, especially for patients who are not receiving neuroleptic medication. With adaptation to the L-DOPA, the movements are reduced while the medication is continued. When the medication is stopped and the patients evaluated 4 weeks later, a reduction in dyskinetic movements was observed and about half the patients showed a marked improvement. Greater improvement was more likely in patients treated at higher doses. The level of improvement appears to be independent of whether the patient is also receiving a neuroleptic drug.

Table

Multiple Regression Analysis Termination AIMS[2] is the Dependent Variable Base AIMS[2] and Total Dose are Stepped

		Total		Facial	
AIMS[2]		r	F	r	F
1. Base AIMS[2]	$r_{1.2}$	-.28		-.21	
2. Total Dose	$r_{1.3}$	.63		.72*	
3. Term AIMS[2]	$r_{2.3}$	.51	3.01	.52	5.50*
	R^2	.52		.67	

*Contributes to prediction of Y p .05.
NOTE: AIMS[2] refers to the squared score referred to in the text.

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Free Communications—Session B

Chair: **Thomas H. Crook, Ph.D.**
Center for Studies of the Mental Health of the Aging
Rockville, Maryland

and

Richard Marcus, Ph.D.
Clinical Service Research Review Branch
National Institute of Mental Health
Rockville, Maryland

*Differential Effects of Trazodone and Amitriptyline on Cognition in Normal Elderly
R.J. Branconnier, D.R. DeVitt, J.O. Cole, and K.F. Spera
Institute for Psychopharmacologic Research, Boston, MA

Combination Choline-Piracetam Treatment of Senile Dementia
Steven H. Ferris, Barry Reisberg, Eitan Friedman, Michael K. Schneck, Kathleen A. Sherman, Pervez Mir, and Raymond T. Bartus
New York University Medical Center, New York, NY

*Loxapine in Psychogeriatrics: A Placebo and Standard Controlled Clinical Study
W.M. Petrie, T.A. Ban, S. Berney, W. Guy, M. Ragheb, W.H. Wilson, and J.D. Schaffer
Tennessee Neuropsychiatric Institute and Vanderbilt University, Nashville, TN

Development and Prediction of Postpsychotic Depression in Neuroleptic-Treated Schizophrenic Patients
Joanne B. Severe, Michel R. Mandel, and Nina R. Schooler
National Institute of Mental Health, Rockville, MD, and Pacific Medical Center, San Francisco, CA

Plasma Levels of Thiothixene by Radioreceptor Assay and Clinical Outcome
Theodore van Putten, Philip R.A. May, Stephen R. Marder, and Jeffery N. Wilkins
Brentwood VA Medical Center and UCLA School of Medicine, Los Angeles, CA

The Effects of Psychotropic Drugs on Informed Consent
Barbara Stanley, Michael Stanley, Eric Peselow, Adam Wolkin, Steven Deutsch, Laura Platt, Julie Speicher, Lynn Golash, and Michael Kaufman
Wayne State University School of Medicine, Detroit, MI; New York University School of Medicine, New York, NY; and Massachusetts General Hospital, Harvard Medical School, Boston, MA

Research Use of the ECDEU Data Bank
John E. Overall and Howard M. Rhoades
The University of Texas Medical School, Houston, TX

DSM-III and the Children's Psychiatric Rating Scale
Betty Pfefferbaum and John E. Overall
The University of Texas Medical School, Houston, TX

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* Denotes paper was presented at NCDEU meeting but not received before going to press.

Haloperidol in Autistic Children: Effects on Learning, Behavior, and Abnormal Involuntary Movements
Magda Campbell, Lowell T. Anderson, Ira L. Cohen, Richard Perry, Arthur M. Small, Wayne H. Green, Lillian Anderson, and William H. McCandless, Jr.
New York University Medical Center, New York, NY

A Controlled Study of Methylphenidate in Combination with Academic Instruction
Rachel Gittelman
New York State Psychiatric Institute, New York NY

Methylphenidate in Adults with Minimal Brain Dysfunction Symptomatology
Jeffrey A. Mattes, Lane Boswell, and Herman Oliver
Bronx VA Medical Center, Bronx, NY, and Long Island Jewish-Hillside Medical Center, Glen Oaks, NY

*The Long-Term Efficacy of Methylphenidate: Medicated vs. Unmedicated Hyperactive Boys at Adolescent Followup
J. Loney, J. Kramer, and T. Kosier
University of Iowa, Iowa City, IA

Combination Choline/Piracetam Treatment of Senile Dementia[1]

Steven H. Ferris, Ph.D.,[2] Barry Reisberg, M.D.,[2] Eitan Friedman, Ph.D.,[2] Michael K. Schneck, M.D.,[2] Kathleen A. Sherman, Ph.D.,[2] Pervez Mir, M.A.,[2] and Raymond T. Bartus, Ph.D.[2]

Despite the compelling rationale for precursor therapy of Primary Degenerative Dementia (PDD, also known as Alzheimer's disease) a large number of clinical trials have failed to demonstrate a consistent pattern of clinically significant effects for either choline or lecithin (Ferris, Sathananthan, Reisberg, & Gershon, 1979; Pomara, Reisberg, Ferris, & Gershon, 1981). Similarly, treatment with the "metabolic enhancer" Piracetam alone also does not appear to improve the cognitive symptoms of senile dementia (Reisberg, Ferris, Schneck, et al., 1981). However, the possibility exists that drugs which enhance brain metabolism might potentiate the effects of cholinergic precursors (Ferris, 1981; Gibson, Shimada, & Blass, 1978). Bartus, Dean, Sherman, & Friedman (1980) treated aged rats with both choline and Piracetam, and demonstrated a synergistic effect on memory retention. Since brain metabolism is reduced in aging and dementia (Ferris, de Leon, Wolf, et al., 1980; Smith, Goochee, Rapoport, & Sokoloff, 1980; Sokoloff, 1979), it may be that a general increase in metabolism improves the possibility of increasing acetylcholine synthesis. Piracetam may also have more direct cholinergic effects, since it increases the incorporation of ^{32}P into phosphatidyl choline (Woelk, 1979) thus suggesting an increase in phosphatidyl choline turnover. We therefore conducted an initial clinical trial in dementia with combination choline/Piracetam treatment.

[1]Supported by USPHS Grants MH-2959 and AGO-1344.
[2]Department of Psychiatry, New York University Medical Center, New York, NY 10016.

Method

Subjects

A total of 15 outpatients, aged 60-85, with a Diagnostic and Statistical Manual-III (DSM-III) diagnosis of PDD completed the study. The patients all showed objective evidence of very mild to moderate cognitive impairment secondary to PDD. The diagnostic evaluation was based on DSM-III criteria and included a medical history,

Development and Prediction of Postpsychotic Depression in Neuroleptic-Treated Schizophrenic Patients

Joanne B. Severe, M.S.,[1] Michel R. Mandel, M.D.,[2] and Nina R. Schooler, Ph.D.[1]

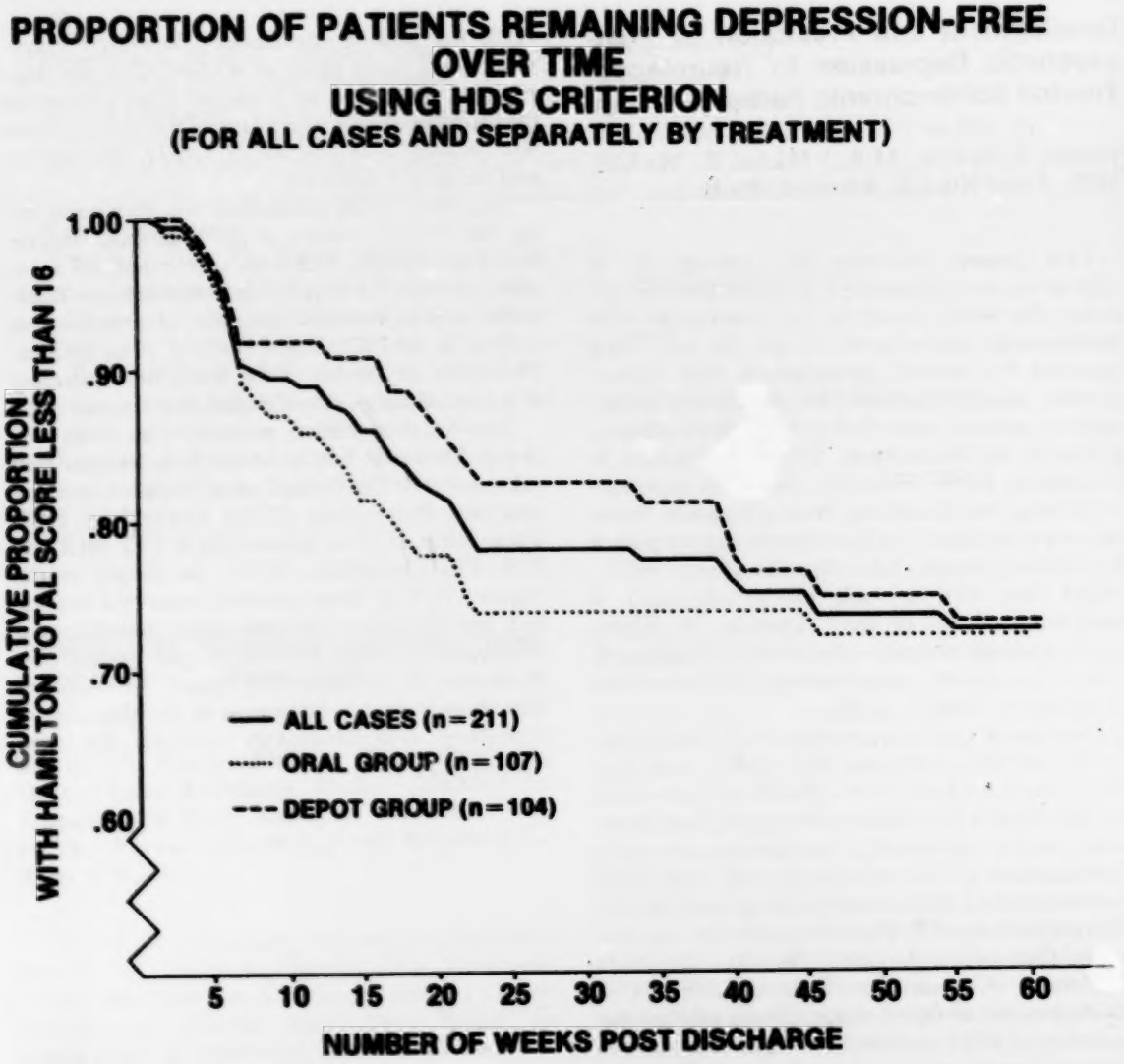
This paper concerns the emergence of depressive symptomatology in schizophrenic patients who were treated in the community with maintenance neuroleptic drugs. It has been reported by several investigators that schizophrenic patients demonstrate depressive symptoms at various times during their illness (Stern, Pillsbury, & Sonnenberg, 1972; McGlashan & Carpenter, 1976). However, there are problems in defining and describing these symptoms. Some investigators claim that such symptoms are part of the natural course of the disorder (Roth, 1970), others that they are side effects (akinesia) of neuroleptic drugs (Rifkin, Quitkin, & Klein, 1975), and still others feel that such symptoms call the diagnosis of schizophrenia into question (Goplerud & Depue, 1978).

Because of reports of postpsychotic depression (PPD) in the literature, data were examined which were available from a National Institute of Mental Health (NIMH) multicenter collaborative trial which specifically compared injectable fluphenazine (FPZ) decanoate with oral FPZ hydrochloride (HCl) in outpatient schizophrenics being maintained in the community for up to 1 year (Schooler, Levine, Severe, Brauzer, DiMascio, Klerman, & Tuason, 1980). This study was not designed to specifically address the question of PPD and therefore lacks the placebo control necessary to determine whether the emergence of depressive symptoms is a result of neuroleptic therapy or is a part of the natural course of the disorder. However, the data can address the following questions: What is the rate of emergence of depression in FPZ-treated schizophrenic outpatients over the course of 1 year? Is this rate higher in patients treated with FPZ decanoate than in those treated with oral FPZ HCl? Are patients who develop depressive symptomatology more likely to relapse? Can development of depression be predicted from presenting psychopathological symptoms at the time patients were acutely ill or from social, family, psychiatric, and treatment histories?

Depressive symptomatology was measured using the 22-item version of the Hamilton Depression Scale (HDS). The scale was completed at intake, at start of community maintenance treatment, and at 4-month intervals. Depression was defined as an HDS Total Score of 16 or greater. Therefore, depression, here, is not the equivalent of a clinical diagnosis of depressive disorder.

Two-hundred eleven patients who were discharged from the hospital depression free and had subsequent HDS ratings were included in these analyses. Forty-seven (22%) attained an HDS Total Score of 16 or greater (25% FPZ HCl and 22% FPZ decanoate, N.S.). As shown in the Figure, 73% of these patients remained depression free and most of the depression that did occur developed by about the fifth to sixth month post discharge. In addition, the Figure demonstrates that there were no differences in development of depressive symptomatology between the drug treatment groups.

[1]Pharmacologic and Somatic Treatments Research Branch, National Institute of Mental Health, Rockville, MD 20857.
[2]Department of Psychological Medicine, Pacific Medical Center, San Francisco, CA 94120.



FIGURE

Comparison between the depressed and nondepressed patient groups revealed that the depressed patients were significantly more likely to relapse (64%) than were the nondepressed patients (19%). In one-third of the depressed patients who relapsed, depressive symptoms and the need to treat them were mentioned as part of the reason for the termination. Therefore, development of depression is a clinically important factor in the failure of the study treatments for these patients.

Further comparisons between the depressed and nondepressed patient groups with regard to baseline symptomatology revealed that when there were differences between the groups, depressed patients had less florid psychotic symptomatology as measured by grandiosity, uncooperativeness, and excitement on the Brief Psychiatric Rating Scale, but not greater despondency of mood. In addition, depressed patients exhibited more somatic symptoms as measured by the HDS at baseline. With regard to

computerized tomography scan, medical and neurological examinations, clinical laboratory tests, psychiatric evaluations, and objective cognitive tests which included the Guild Memory Scale (Crook, Gilbert, & Ferris, 1980). Patients with a Hamilton Depression Scale score greater than 18 were excluded. The patients selected had Global Deterioration Scale scores of 2-4 (Reisberg, Ferris, de Leon, & Crook, in press).

Procedure

This was an open study designed to verify the safety and tolerance of combined choline/Piracetam treatment, and to obtain preliminary evidence as to possible efficacy. Patients received 9 g/d of choline chloride and 4.8 g/d of Piracetam for a period of 7 days. A short cognitive test battery (Buschke task, First-Last Names, facial recognition, Digit Symbol Substitution Test and tapping speed) and behavioral rating scales (IPSC-E psychiatrist's scale and MS-E self-rated mood scale) were administered at baseline and following the treatment period. Plasma and red blood cell (RBC) choline levels were also determined for 10 of the 15 subjects.

Results and Discussion

No side effects were reported. For the entire group, most cognitive measures showed small, nonsignificant improvements. Some subjects showed no changes, but none were worse. Since the study psychiatrist independently rated four patients as clinically improved, the cognitive measures for these patients were analyzed separately. The results for the Buschke Selective Reminding Task are shown in Figure 1. Each patient showed marked improvement in memory storage and retrieval. These "responders" were all subjects with moderate rather than very mild cognitive impairment. We have not previously observed such marked clinical improvements with choline treatment alone (Ferris et al., 1979; Ferris et al., 1981) or Piracetam treatment alone (Reisberg et al., 1981).

The results for the blood choline assays are shown in Figure 2. Of the 10 subjects for whom data were available, all showed marked increases

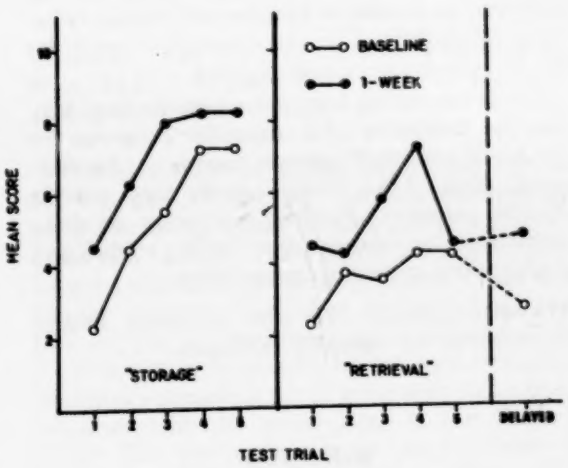


FIGURE 1. Mean scores for "storage" and "retrieval" on the Buschke Selective Reminding Task for the treatment "responders" ($N=4$) before and after treatment for 1 week with choline + Piracetam.

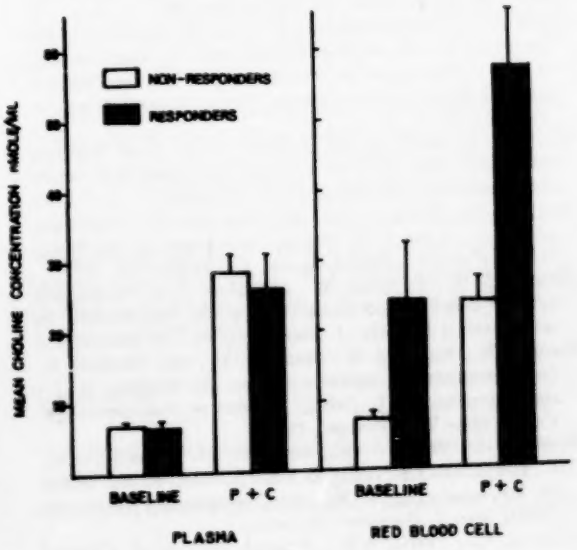


FIGURE 2. Mean (± SEM) plasma and red blood cell choline concentrations for the responders ($N=3$) and nonresponders ($N=7$), before and after 1 week of treatment with choline + Piracetam.

in both plasma and RBC choline levels during treatment. However, the responders showed much higher RBC choline levels than the nonresponders, both at baseline and during treatment (p's $< .025$). The plasma choline levels for the two groups were quite similar.

These interesting but preliminary findings suggest the possibility of a responder subgroup for combined choline/Piracetam treatment. Furthermore, high RBC choline levels may predict clinical response. Further evaluation of these possibilities by means of dose-finding studies and double-blind trials is recommended.

Acknowledgment: We wish to thank Denise Hernaize for her valuable assistance.

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life history characteristics, depressed patients were more likely to have a history of antidepressant and/or stimulant use, have been hospitalized for psychiatric illness in the past more often, and have had the truth about their illness told to family and friends.

The combination of the measures of somatic symptoms, grandiosity, prior use of stimulants, and the veracity of the explanation of the patient's hospitalization accounted for 19% of the variance in the prediction of depression status. Using the jackknife procedure (Mosteller & Tukey, 1977), a technique for replication which provides a more reliable estimate, 13% of the variance in depression status was accounted for. Despite the shrinkage, this is still significant. Thus, these data are able to provide some clues for prospective identification of those schizophrenic patients who will develop depressive symptomatology.

It is clear that depressive symptomatology in schizophrenic patients is a real problem and that more research is needed to better understand the phenomenon. The relationship of depression and relapse highlights the more pressing need for research into treatments for these symptoms.

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Plasma Levels of Thiothixene by Radioreceptor Assay and Clinical Outcome[1]

Theodore van Putten, M.D.,[2] Philip R.A. May, M.D.,[2] Stephen R. Marder, M.D.,[2] and Jeffrey N. Wilkins, M.D.[2]

If plasma levels of antipsychotic drug were to relate to clinical outcome, the pharmacotherapy of schizophrenia might become less of a frontier profession. So far, research on the relationship between plasma levels of antipsychotic drugs and clinical outcome has been disappointing. On balance, few relationships have been found. This could be due to design deficiencies such as flexible dosage or contamination by other treatments or to problems with the assay (May & van Putten, 1978). The new radioreceptor assay (Creese & Snyder, 1977) appears simple to perform, sensitive, and suitable for routine clinical use.

The obvious question is whether the radioreceptor assay is clinically useful: specifically, does the assay correlate with clinical outcome or side effects?

Method

Thirty-four newly admitted schizophrenic patients who had not taken antipsychotic medication for at least 2 weeks (the majority not for several months) were treated with a fixed dose of thiothixene for 4 weeks. In general, these patients were admitted voluntarily (92%); in young middle age (mean age 32.7 years, SD 9.9); never married (50%); with a chronic disorder (mean duration of 5.2 years, SD 5.6).

Treatment

A fixed thiothixene dosage was given daily for 4 weeks at bedtime (0.44 mg/kg or 0.2 mg/lb). If there had been a serious toxic reaction to the first

[1]This research was supported by the Veterans Administration Medical Research Service.

[2]Veterans Administration Medical Center, Brentwood and UCLA School of Medicine, Los Angeles, CA 90024.

Address correspondence to Dr. van Putten at: VA Medical Center Brentwood, 11301 Wilshire Blvd., Los Angeles, CA 90073.

dose, the dosage was fixed at a lower level. Antiparkinson drugs were given if extrapyramidal side effects were troublesome.

Thiothixene Assay

Thiothixene and its active metabolites were measured in plasma by Creese and Snyder's radioreceptor technique in which the added drug competes with [^{3}H]-spiperone for binding to dopamine receptors in calf caudate membranes (Lader, 1980).

Dopamine receptor-blocking activity of drug in the plasma samples was expressed as neuroleptic units (n.u.). One n.u. is defined as the amount of displacement of tritiated spiperone produced by 1 nmole of haloperidol.

The lower limit of sensitivity is 15 n.u.

Outcome Measures

Clinical outcome was measured before and after treatment on the Brief Psychiatric Rating Scale (BPRS) (completed by the psychiatrist) and by a Clinical Global Improvement Scale (CGI) and the Nurses' Observation Scale for Inpatient Evaluation (NOSIE) taking change in total score from baseline to the end of treatment as the criterion. The raters were blind to the plasma measurements.

Results

Relation to Outcome

Figure 1 shows the relationship between the nurses' global improvement ratings and plasma level. Improvement occurred over the entire range of recorded plasma levels, but the chances of substantial improvement appear greater above 40 n.u. If the sample is dichotomized to compare (very much + much improved) vs. (minimally improved + no change) with 40 n.u. as the criterion, chi square = 6.05, $p < .01$. The results with physician's global improvement ratings showed a similar trend, but the chi-square missed statistical significance.

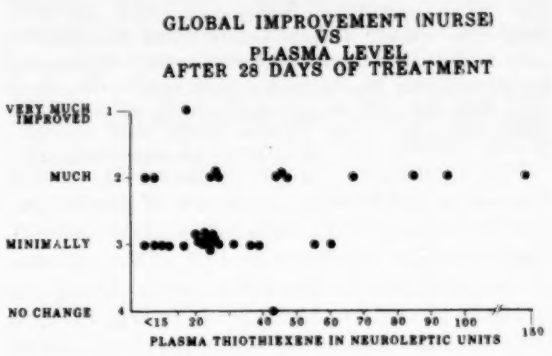

FIGURE 1

Figures 2 and 3 show the relationship between the NOSIE and BPRS change scores and plasma level. The trend is the same: improvement occurs over the entire recorded range of plasma levels, but the chances of substantial improvement appear greater above 40 n.u. It is clear, however, that many patients improved at lower neuroleptic levels; the relationship is far from substantial.

Correlations between plasma levels and outcome (both at 28 days) appear in the Table. Correlations for the doctor's CGI and NOSIE were significant at the .025 level.

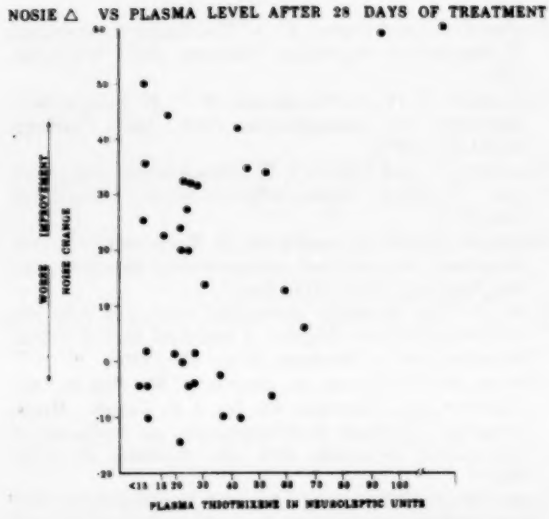
NOSIE Δ VS PLASMA LEVEL AFTER 28 DAYS OF TREATMENT
WORSE IMPROVEMENT
NOSIE CHANGE
PLASMA THIOTHIXENE IN NEUROLEPTIC UNITS

FIGURE 2

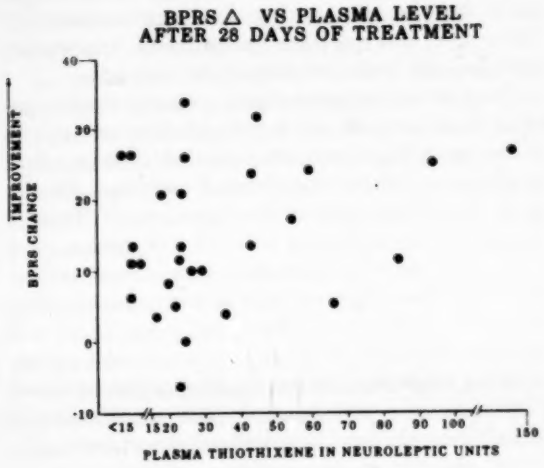

FIGURE 3

Relation to Side Effects

There was no consistent relationship between side effects after 4 weeks of treatment and plasma level. Some of the highest drowsiness ratings occurred in those with very low plasma levels. Similarly, there was no consistent relationship between akathisia or akinesia and plasma level.

Dosage and Outcome

There was no relationship between dosage (either mg or mg/kg) and any of the four outcome measures.

Discussion

The findings indicate that improvement is more likely at higher plasma levels (>40 n.u.) of thiothixene. Many, however, improved at very low plasma levels. Indeed, two of the six who improved at plasma levels < 15 n.u., had an illness which, in the past, responded only to an antipsychotic drug.

The data do not support the notion of a "therapeutic window" in that higher plasma levels were not associated with side effects or clinical deterioration (although at extreme plasma levels this must of course be so). In fact, an additional four patients who improved markedly only on very high doses (60, 120, 120, and 160 mg of thiothixene) had high plasma levels (65, 78, 170, and 140 n.u., respectively). Again, higher plasma levels appear associated with improvement, as long as the patient can tolerate them!

In 11 of 20 nonresponders, dosage could not be increased because of akathisia, drowsiness, or akinesia, either singly or in combinations. A plasma level of thiothixene may be particularly useful in the nonresponder with troublesome side effects. If such a nonresponder has a low plasma level (< 40 n.u.), it would seem prudent to switch to another antipsychotic drug.

Table

Correlations (*r*) Between 28-Day Plasma Levels of Thiothixene and Outcome

	CGI Nurse	CGI Doctor	NOSIE	BPRS
r	.260	.358	.363	.289
p	n.s.	.025	.025	.05

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The Effects of Psychotropic Drugs on Informed Consent[1]

Barbara Stanley, Ph.D.,[2] Michael Stanley, Ph.D.,[2] Eric Peselow, M.D.,[3] Adam Wolkin, M.D.,[3] Steven Deutsch, M.D.,[3] Laura Platt, M.S.W.,[3] Julie Speicher, M.D.,[3] Lynn Golash,[3] and Michael Kaufman, M.D.[4]

Acutely psychotic patients are frequent candidates for research projects which attempt to find more efficacious pharmacologic treatments for their conditions. These patients are often the only appropriate group for the final stage of testing the treatments. However, there is a good deal of concern about the abilities of hospitalized psychiatric patients to give consent. This concern is reflected by their status as a vulnerable population in the proposed regulations for the institutionalized mentally disabled (*Federal Register*, 1978). This classification deems them as needy of special protection. While there are many different opinions about the extent of their vulnerability, there are little empirical data which confirm the need for this proposed special protection.

Earlier research investigating this issue found that severely ill psychiatric patients perform as wellin the consent process as hospitalized medical patients (Stanley, Stanley, Schwartz, 1980; Stanley, Stanley, Lautin, Kane, & Schwartz, 1981). These findings indicated that it was important to look more closely at consent with the mentally ill.

Issues such as the differential effects of diagnosis, mood, and length of hospitalization on competency are in need of investigation. Further, there remains a question about the effect of psychotropic medication on patients' competency. Some have argued that patients would alter their opinions about participation in research or become more competent following stabilization on psychotropic drugs. On the other hand, it has also been argued that a consent obtained under the influence of psychotropic drugs can never be valid because the patient is "mind-controlled." Therefore, this question has practical importance with respect to the timing of the consent.

Does an investigator obtain consent while a patient is acutely ill, or should he first attempt to bring the symptoms under control with standard treatments, obtain the consent, washout the patient, and then conduct the experiment? This, of course, is procedurally difficult. However, if it can be demonstrated that patients make more rational decisions about research participation when they are medicated, then the procedural difficulties might be justified for the sake of a significant improvement in the quality of the consent. Therefore, the present study was undertaken to determine whether hospitalized psychiatric patients' abilities to give consent, change over the course of treatment—prior to a drug regimen and after stabilization on psychotropic medication.

In this preliminary study, the following questions were addressed: 1) do severely ill psychiatric patients alter their opinions with respect to their willingness to participate in a series of research projects with varying risk/benefit ratios prior to drug treatment and after becoming stabilized? 2) does comprehension of consent information increase following drug treatment? 3) does rationality or reasoning about their decision to participate or not participate improve after drug treatment? and 4) for those patients who changed their minds, did they become more reasonable in their decisions?

Method

In order to assess the effects of psychotropic medication on ability to give valid consent, a series of four hypothetical vignettes were administered to psychiatric patients prior to drug treatment and following treatment. Two of the vignettes were alternate forms of one high-risk/low-benefit vignette and one low-risk/high-benefit vignette. The other two vignettes were both administered twice. Patients' competency to give consent was assessed on four separate dimensions which represent common notions of competency (Sullivan, 1974; Friedman, 1975; Roth, Meisel, & Lidz, 1977): evidencing a choice;

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[2]Psychiatry, Ethics, and Law Program, Psychiatry Department, Wayne State University School of Medicine, Detroit, MI 48206.

[3]New York University School of Medicine, New York, NY 10016.

[4]Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114.

reaching a reasonable decision; comprehending the consent information; and reasoning in a rational manner about the decision.

In order to determine whether the patients' psychiatric conditions improved, a psychiatrist independently assessed the patients on admission and again at the time of the second competency interview. The Brief Psychiatric Rating Scale (BPRS) was utilized for the psychopathology assessments.

The sample was comprised of 39 psychiatric inpatients on a locked unit at Bellevue Psychiatric Hospital. All were interviewed within 72 hours after admission and again just prior to discharge. In most cases, patients were discharged within a day after the final assessment. When patients were not immediately discharged, it was usually as a result of disposition problems. Twenty-seven patients received psychotropic medication and 12 patients were unmedicated and served as a comparison group to control for the effects of hospitalization.

Table 1 shows the diagnostic categories into which the medicated patients fell. All but one—the personality disorder—fell into the range of very severe psychiatric illness. Table 2 shows that the medications these patients were taking at the time of discharge were the standard psychotropic drugs. The length of time patients were medicated coincides with the length of hospitalization ($\overline{X}$ = 27 days; SD = 12.6).

All medicated patients were judged by the treating psychiatrist to be stabilized on medication by the final competency assessment.

Table 1

Diagnosis

(N = 27)	Percent	N
Schizophrenic Disorder	48.2	13
Psychotic Disorder	33.3	9
Affective Disorder	14.8	4
Personality Disorder	03.7	1

Table 2

Medication on Discharge (N–22)

	N
Prolixin Decanoate (12.5-75 mg)	5
Trilafon (16-48 mg)	4
Mellaril (300 mg)	2
Stelazine (10-40 mg)	2
Lithium (1,200-1,800 mg) and Trilafon (8-48 mg)	2
Haldol (2.5-30 mg) and Lithium (900-2,100 mg)	2
Haldol (5 mg) and Elavil (25 mg)	1
Lithium (900 mg) and Thorazine (200 mg)	1
Haldol (15 mg)	1
Lithium (900 mg)	1
Thorazine (1,000 mg)	1

Table 3

Patient Responses Prior to and Following Drug Treatment (N = 27)

	Time 1-Time 2 Yes-Yes %	Time 1-Time 2 No-No %	Time 1-Time 2 Yes-No %	Time 1-Time 2 No-Yes %
High Risk/Low Benefit Studies*	14.8	37.0	25.9	22.3
	51.8		48.2	
Low Risk/High Benefit Studies*	51.8	14.8	18.5	14.8
	66.7		33.4	
Moderate Risk/High Benefit	3333	33.3	11.1	22.3
	66.6		33.4	

* Alternate forms

Results

To determine the effect of drugs on decisions about research participation, patients' responses to the hypothetical studies were analyzed. Responses prior to drug treatment and following treatment were compared. The percentage of patients who did not alter their opinions and those who did are presented in Table 3.

For the high-risk/low-benefit studies, about 15% of the patients agreed to participate both before and after treatment, while 37% refused both times. In this case, refusal would be the reasonable decision, because of the unfavorable risk/benefit ratio. Twenty-six percent changed from agreeing to refusing and about an equal percentage (22%) changed in the opposite direction from a reasonable or "good" decision to a poor choice. A statistical test of the difference in proportions for the four possible comparisons shows no significant differences among the proportions (HR/LB Study – $z = .39$, $N = 27$, NS). Thus, for the first study, patients do not become more or less reasonable in their decisions as a result of treatment.

This was also true for the other three vignettes (LR/HB Study $z = .27$, $N = 27$, NS; HR/HB Study $z = .14$, $N = 18$, NS; MR/HB Study $z = .85$, $N = 18$, NS). There was no significant directional change following any treatment. When patients change their minds, about an equal percentage moves in either direction. It is particularly striking to note about the last three vignettes that two-thirds of the patients do not change their minds at all. This suggests that drug treatment does not alter patients' decisions about research.

In comparing the drug-treated group with the group of patients who received no medication during their hospitalization, no significant differences emerged in willingness to participate in hypothetical studies. (Final Interview - HR/LB Study $x^2 = <1$, $N = 39$, NS; LR/HB Study $x^2 = <1$, $N = 39$, NS; HR/HB Study $x^2 = <1$, $N = 27$; MR/HB Study $x^2 = <1$, $N = 27$, NS).

Differences in comprehension of the consent information prior to and following drug treatment were also examined. Comprehension did not improve significantly ($t = 1.81$, $df = 17$, NS). An additional analysis of the patients' stated reasons for participation or refusal, revealed that the quality of reasoning about the consent decisions showed no significant improvement following treatment ($t = 1.57$, $df = 17$, NS). These findings are noteworthy because psychopathology decreased significantly (Initial BPRS scores $\overline{X} = 43.5$, S.D. = 9.1; final BPRS scores $\overline{X} = 38.3$, $SD = 7.9$; $t = 3.52$, $N = 27$, $p < .01$). Thus, although patients' conditions improved, their competency did not. This is consistent with previous findings which suggest that psychopathology does not correlate with ability to give consent (Stanley et al., 1981).

In conclusion, these preliminary results seem to indicate that the quality of consent does not improve following drug treatment. These data do not lend support to the notion that patients should be stabilized on standard drugs prior to enlisting them as subjects. Additional data are now being collected to determine whether these preliminary results will remain the same with a large sample.

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Research Use of the Early Clinical Drug Evaluation Unit Data Bank

John E. Overall, Ph.D.,[1] and Howard M. Rhoades, M.A.[1]

The purpose of this brief report is to indicate one way in which the research potential of the Biometrics Laboratory Early Clinical Drug Evaluation Unit (ECDEU) data bank has been used for general methodological investigations. The Biometrics Laboratory at George Washington University provided a statistical data-analysis service for investigators in the ECDEU and New Clinical Drug Evaluation Unit (NCDEU) programs for almost a decade. During that time, a valuable data bank consisting of rating scales and other descriptive information on large numbers of patients was acquired. As far as the present report is concerned, it is important to emphasize that the data bank pertains specifically to patients who were subjects in clinical psychopharmacology research.

A problem in dealing with a data bank of this magnitude is that different studies use different rating scales and have differing protocols. In order to effectively manage this amount of data, an extraction was made so that each subject would have comparable data in a standard format. Patients included in this extraction were required to have at least the demographic information, a pretest rating on the Brief Psychiatric Rating Scale (BPRS), and a rating on the BPRS that fell 6 to 12 weeks after the onset of the clinical trial. The data to be presented refer to those patients and to studies that included a minimum sample size of at least six per group. Studies in which the BPRS was not used and studies with very small sample sizes were not included.

The first question that was asked of the derived data file concerned how many different drug treatment *populations* are represented. For this purpose a "drug treatment population" was defined as the population from which subjects for a particular study were drawn, and two studies were considered to involve the same drug treatment population if the mean symptom profiles for patients in the studies were similar. A multidimensional scaling of mean pretreatment BPRS profiles revealed two major clusters, one including studies of antipsychotic drugs and the other including studies of antidepressant/antianxiety drugs.

The fact that the data bank consists of two major treatment populations does not imply that individual patients within those treatment populations are phenomenologically homogeneous. An iterative profile analysis method was used to define BPRS profile patterns that are maximally representative of four phenomenological subtypes of depressive disorders within the one treatment population and maximally representative of four phenomenological subtypes of thinking disorder psychoses within the other treatment population. Depressive disorders are characterized as anxious, hostile, retarded, or agitated; and thinking disorder psychoses are characterized as florid, withdrawn-disorganized, hostile-suspicious, or agitation-excitement types. Although this typology of major psychiatric disorders is not new, its refinement to be maximally representative of patients in the ECDEU data bank is considered pertinent to further clinical psychopharmacology research.

Classification functions, which are simple weighted combinations of BPRS symptom ratings (scored 0 to 6), can be used to assign individuals among the eight phenomenological types. The weighting coefficients derived from the ECDEU data bank are presented in the Table. To classify an individual patient, one simply calculates the eight different weighted sums of his/her BPRS symptom ratings and assigns the individual to the group for which the weighted sum is greatest. This is one of several ways that phenomenological classification can be objectively achieved from analysis of BPRS profiles. It is a very simple matter to write a computer program that will calculate the weighted sums, given the classification function coefficients presented in the Table.

Given the ability to assign individual patients among the eight phenomenological types, several issues related to clinical drug trials were investigated. The percentages of good response to placebo were examined across 6 controlled trials of presumed antidepressant drugs and 17 placebo-controlled trials of presumed antipsychotic drugs.

[1]The University of Texas Medical School, Houston, TX 77025.

Table

Classification Functions for Eight Phenomenological Types

Phenomenological Type	BPRS Symptom																		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Constant
Anxious Depression	.264	.640	.294	-.156	.333	.629	-.146	.290	2.012	-.057	-.142	-.297	-.506	.193	-.251	.086	-.377	-.045	-8.755
Retarded Depression	.302	.592	.490	-.405	.188	.513	-.006	.444	1.874	.101	-.260	-.360	.929	-.111	-.279	.241	-.425	.091	-9.631
Agitated Depression	.270	.465	-.058	-.381	.549	.835	-.354	.220	1.886	-.208	-.142	-.336	-.201	-.151	-.016	.029	1.723	-.123	-11.153
Hostile Depression	.117	.628	.134	-.369	.722	.766	-.142	-.012	1.558	2.156	-.158	-.367	.089	-.399	-.211	-.065	-.242	-.026	-11.386
Florid Thinking Disorder	.023	.191	.495	.555	-.071	.453	.170	.244	-.351	-.048	.139	.451	-.013	-.825	1.256	.523	-.056	-.241	-8.590
Withdrawn-Disorganized	-.102	.331	1.136	.142	-.198	.251	.378	.302	-.107	-.221	-.140	-.180	.262	-.424	-.350	1.044	-.346	.418	-7.344
Agitated Excitement	.228	.673	.005	.160	.016	.656	.250	.466	-.023	.573	.209	-.198	-.407	-.138	.677	.098	1.361	-.310	-9.375
Hostile Suspiciousness	.296	.740	.521	.058	-.075	.458	.102	.055	.237	.732	1.105	-.410	.145	.064	.664	.459	-.282	-.391	-9.503

The placebo response rate for anxious and hostile depression subtypes was approximately two-thirds, whereas the placebo response rates for retarded and agitated depressions was only about one-third. Across a larger pool of studies, the response rate for all four depressive subtypes to active medications was approximately two-thirds. Although the placebo patients were not concurrent controls in most of the same studies from which the drug-treated patients came, the pattern of response across depressive subtypes does seem to suggest that it may be more difficult to show a true treatment effect in the anxious and hostile subtypes of depressive disorder because of the good placebo response of such patients.

The same comparisons of response rates were made for placebo and active drug groups in the pool of antipsychotic drug trials from the ECDEU data bank. Placebo response rates ranged from 6 to 29% for the four thinking disorder syndromes. The response rates for florid thinking disorder, agitation-excitement, and hostile-suspiciousness syndromes were two to four times greater in the active medication pool than in the placebo pool. By way of contrast, the response rate for the withdrawn-disorganized type was approximately 9% in both the placebo and active drug pools. Again, the placebo patients were not concurrent controls for most of the active medication patients in the pooled data; however, comparison of response rates across phenomenological subtypes suggests that withdrawn-disorganized thinking disorder may not be a good type of patient for demonstrating clinical efficacy of antipsychotic medications because of the low rate of favorable response to both drug and placebo.

Many other and perhaps more interesting uses can be made of the ECDEU data bank. The main intent of this brief report is to emphasize the advantage that can derive from large accumulations of similar data from many small clinical trials. Individual trials usually do not involve sample sizes adequate to examine many issues of both methodological and clinical importance. Centralized facilities that provide statistical support services are in a particularly strategic position to develop meaningfully large data banks in a variety of research domains, as the ECDEU data bank exemplifies in clinical psychopharmacology.

Diagnostic and Statistical Manual-III and the Children's Psychiatric Rating Scale[1]

Betty Pfefferbaum, M.D.,[2] and John E. Overall, Ph.D.[2]

The purpose of this investigation was to identify primary dimensions of manifest psychopathology that distinguish among different emotional and behavioral disorders of childhood and to identify the Diagnostic and Statistical Manual-III (DSM-III) diagnoses for which each of the primary dimensions is particularly relevant. The Children's Psychiatric Rating Scale (CPRS) provides for assessment of a broad range of symptoms and behaviors related to childhood psychopathology (Guy, 1976). It consists of 63 symptom and behavior constructs which are rated on seven-point scales of severity. It was used in this investigation because it preceded the development of DSM-III and provides a description of the major emotional and behavioral components of childhood diagnoses using terms other than the specific criteria listed in DSM-III. The methodology of factor analysis was used to identify clusters of correlated symptom and behavior variables that define major dimensions of difference among diagnostic groups in the CPRS measurement space.

Five child and adolescent psychiatrists were asked to provide descriptions of what they considered, from their clinical experience, to be typical patients belonging to each of 18 DSM-III diagnostic categories. The descriptions were recorded as ratings of symptom severity on the 63 scales of the CPRS. The psychiatrists were asked to describe levels of severity for all associated symptoms as well as for primary target symptoms of each disorder.

A cluster-oriented multiple-group method of factor analysis was used to identify subsets of variables that tend to represent independent aspects of the symptom domain. Seven independent dimensions were identified. The factors were

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[2]Department of Psychiatry, The University of Texas Medical School, Houston, TX 77025.

then rotated to an oblique simple structure in which each CPRS variable tended to relate clearly to one and only one of the seven references axes (Overall, 1974). The seven factors were interpreted as representing behavioral problems, depression, thought disturbance, psychomotor excitation, psychomotor retardation, nervousness/tension, and organicity.

A single CPRS profile to represent each of the 18 diagnostic concepts was calculated by averaging across the five raters. A transposed (Q-type) factor analysis of the 18 diagnostic profiles resulted in identification of six distinct clusters which are presented in Table 1. This analysis provided a basis for grouping together the DSM-III diagnoses that tend to share predominant features of the total symptom and behavior profile pattern, while disregarding specific distinctions that contribute little to the overall differences in symptom profile patterns. The diagnosis oppositional disorder did not clearly relate to only one cluster but related to the cluster including the conduct disorders and the cluster including the anxiety disorders. It was, therefore, not included in any one cluster.

Table 1

Cluster	DSM-III Diagnosis and Code
I	Conduct Disorder, Undersocialized, Aggressive (312.00)
	Conduct Disorder, Undersocialized, Nonaggressive (312.10)
	Conduct Disorder, Socialized, Aggressive (312.23)
	Conduct Disorder, Socialized, Nonaggressive, (312.21)
II	Infantile Autism (299.0x)
	Childhood Onset Pervasive Development Disorder (299.9x)
	Schizophrenic Disorder (undifferentiated) (295.9x)
III	Separation Anxiety Disorder (309.21)
	Overanxious Disorder (313.00)
	Identity Disorder (313.82)
	Anorexia Nervosa (307.10)
IV	Attention Deficit Disorder with Hyperactivity (314.01)
	Attention Deficit Disorder without Hyperactivity (314.00)
V	Avoidant Disorder (313.21)
	Schizoid Disorder (313.22)
	Elective Mutism (313.23)
VI	Major Depression (296.2x)
	[Oppositional Disorder (313.81)]

The empirical clustering of symptom rating scale profiles produced a classification of disorders that generally corresponds to the major diagnostic groupings in DSM-III. The diagnostic clusters share enough of the total range of symptom manifestations to have highly similar factor score profiles and can be considered on empirical grounds to represent the major syndromes of childhood psychopathology. From the point of view of treatment evaluation, the clusters of specific diagnoses share enough common symptomatology to be evaluated along the same major dimensions.

The one or two discrepancies between the DSM-III classification of childhood diagnoses and the empirical grouping based on similarities of CPRS symptom and behavior rating profiles highlight the distinction between underlying dynamics and descriptions of behavior. For example, the diagnosis avoidant disorder is classified with the anxiety syndromes in DSM-III. The overt behavioral manifestations, however, primarily involve diminished social interaction. Elective mutism represents an extreme example of such behavioral manifestations. The CPRS profile places avoidant disorder with elective mutism and schizoid disorder in recognition of the manifest social withdrawal rather than with the anxiety disorders, even though anxiety may indeed by the underlying basis for the manifest behavior. Regardless of the DSM-III classification, it is apparent that the manifest psychopathology associated with avoidant disorder was considered by these psychiatrists to be represented in rating scale terms along the same primary dimensions that are useful in characterizing other forms of social and behavioral withdrawal. Another interesting difference between the DSM-III classification and this one is that anorexia nervosa and identity disorders are included in the category of anxiety disorders in this grouping. In all other respects the empirical classification based on complete CPRS profile patterns appears consistent with the DSM-III grouping of specific diagnoses into broader categories.

Based on examination of the mean factor score profiles for diagnostic groups in each of the six major clusters, as well as on clinical experience with the syndromes, specific factors are proposed as relevant for evaluation of psychopathology and measurement of treatment response in different diagnostic groups. These are presented in Table 2. For some clusters, one or two factors appear more relevant than the others and are indicated by an asterisk.

Table 2

Cluster	DSM-III Diagnosis and Code
I:	Conduct Disorders
	Behavioral Problems*
	Psychomotor Excitation
II:	Childhood Psychoses
	Behavioral Problems
	Thought Disturbance*
	Psychomotor Excitation
	Psychomotor Retardation
	Nervous/Tension
	Organicity*
III:	Anxiety Disorders
	Behavioral Problems
	Depression
	Psychomotor Excitation
	Nervous/Tension
IV:	Attention Deficit Disorders
	Behavioral Problems*
	Depression
	Psychomotor Excitation*
	Nervous/Tension
V:	Avoidant Disorders
	Depression
	Psychomotor Retardation*
	Nervous/Tension
VI:	Depression
	Behavioral Problems
	Depression*
	Psychomotor Excitation
	Psychomotor Retardation
	Nervous/Tension

*Greater relevance

The purpose of the cluster analysis was not to encourage use of the rating scale for diagnostic purposes. Results from the cluster analysis provide a guide to the CPRS symptom factors that are relevant for evaluation of levels of severity and treatment response in various DSM-III diagnostic groups. One can expect to measure significant improvement only on those major dimensions of psychopathology that are relevant to the particular diagnostic entities being treated.

In summary, factor analysis of the CPRS has been used to identify clinically meaningful factors and cluster analysis to identify six major clusters of DSM-III diagnostic groups. Examination of the results has led to an identification of the factors that are most relevant for characterizing the patients in each of these six diagnostic clusters. It is suggested that a modification of the CPRS based on this factor analysis could facilitate investigating and documenting psychopathology and treatment response in a more efficient manner.

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Haloperidol in Autistic Children: Effects on Learning, Behavior, and Abnormal Involuntary Movements[1]

Magda Campbell, M.D.,[2] Lowell T. Anderson, Ph.D.,[2] Ira L. Cohen, Ph.D.,[2] Richard Perry, M.D.,[2] Arthur M. Small, M.D.,[2] Wayne H. Green, M.D.,[2] Lillian Anderson, R.N.,[2] and William H. McCandless, Jr., M.A.[2]

The efficacy of haloperidol as one treatment modality for young autistic children has been supported by the results of our two recently published studies (Campbell, Anderson, & Meier, 1978; Cohen, Campbell, & Posner, 1980). Both trials were double-blind and placebo-controlled, and patients were randomly assigned to treatments.

However, the following questions remained unanswered: 1) how does haloperidol facilitate learning—by directly affecting attentional mechanisms or by reducing withdrawal and stereotypies? 2) what are the long-term therapeutic effects of haloperidol? and 3) what are the possible long-term untoward effects, specifically the effects on neuroleptic-induced abnormal movements?

To answer these questions, a double-blind, placebo-controlled trial of haloperidol in 40 autistic children who met the Diagnostic and Statistical Manual-III (DSM-III) criteria was conducted. A total of 33 subjects ages 2.3 to 7.9 years (mean, 4.7 years) have thus far completed the study.

The children were maintained for 2 weeks on placebo for baseline evaluations. Those suitable were randomly assigned to one of two treatment sequences: haloperidol-placebo-haloperidol or placebo-haloperidol-placebo. Each treatment period lasted 4 weeks.

Discrimination learning, behavioral symptoms, and untoward effects were rated. The ratings of the two child psychiatrists using the Children's Psychiatric Rating Scale (CPRS), Clinical Global Impressions (CGI), Abnormal Involuntary Movement Scale (AIMS), and the Abbreviated Dyskinesia Rating Scale (Simpson, Lee, Zoubok, & Gardos, 1979) were videotaped. The results videotaped were as follows.

The optimal doses of haloperidol ranged from 0.5 mg/day to 3.0 mg/day (mean, 1.12 mg/day). At these doses, serum levels of haloperidol ranged from ND* or 1.30 to 8.30 ng/ml (collaborative study with Drs. Robert Rubin and Russell Poland, Torrance, California).

On these doses, haloperidol was found to be significantly superior to placebo in reducing behavioral symptoms on the CGI and the CPRS; specifically, stereotypies, withdrawal, hyperactivity, abnormal object relations, and fidgetiness were lower on drug ($p < .001$) (Figure 1). The placebo scores were significantly higher than haloperidol scores on the Conners' Parent Teacher Questionnaire (PTQ) ($p < .01$). The Timed Behavioral Rating Sheet revealed that the effects on stereotypies were a function of the structure of the rating conditions; in the unstructured rating, mean stereotypy scores remained high across treatment, while in the structured situation stereotypies decreased on haloperidol relative to placebo.

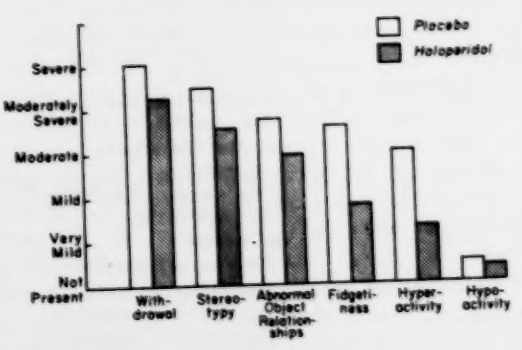

FIGURE 1. Comparison of 33 autistic children receiving placebo vs. haloperidol in terms of their average scores on the Children's Psychiatric Rating Scale. There was a significant difference between groups ($p < .001$) as determined by a matched-pairs signed ranks test, on all items except hypoactivity: children receiving haloperidol were rated to have less severe behavioral symptoms.

[1]This study was supported in part by USPHS Grant MH-32212 from the National Institute of Mental Health. The authors wish to thank McNeil Pharmaceuticals for supplying haloperidol and matching placebo tablets.

[2]Department of Psychiatry, New York University Medical Center, New York, NY 10016.

*ND = < .05 ng/ml.

Administration of haloperidol at these doses not only resulted in reduction of behavioral symptoms, but also facilitated learning in the laboratory situation. There, a computer-controlled operant conditioning apparatus was used to present stimuli, record responses, present reinforcers according to a specified schedule, and record durations of stereotypic behavior; motor activity levels were also recorded from pressure sensors mounted under carpeting.

Children were required to learn that reinforcement was available if the lever was pressed during the presentation of an auditory-visual stimulus pattern (S+) and was not available when the stimulus pattern was off (S−). Discrimination indices were computed for each child and the mean across children plotted as a function of sessions and treatments.

The results indicate that children receiving haloperidol learned the discrimination while those on placebo did not (Figure 2). This was by virtue of the haloperidol group displaying fewer responses when the auditory-visual stimulus pattern was off (S−). Children who acquired the discrimination on haloperidol retained it when placed on placebo. Children shifted from placebo to haloperidol showed continued improvements in performance and decelerations in inappropriate responding which were comparable to the children who acquired the discrimination on haloperidol. Developmental level, *per se*, did not interact with drug to determine performance.

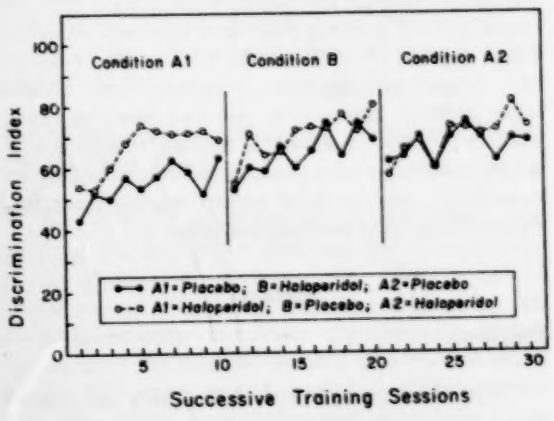

FIGURE 2. Discrimination learning in 22 autistic children during two treatment sequences.

There was no significant effect of medication on stereotypies between the two groups in the laboratory; this suggests that reduction in this symptom is not responsible for the improvement in learning.

The second part of the study was an investigation of long-term effects of haloperidol. If the child responded well to haloperidol during the 12-week trial, he was placed on this drug for an additional 6 months. Children were randomly assigned to one of the two conditions: 5 days of haloperidol and 2 days of placebo (discontinuous treatment), or haloperidol every day of the week (continuous treatment). Every 6 months, haloperidol was discontinued and the child was placed on placebo for 4 weeks. Behavioral ratings on the CPRS and CGI, and ratings on the AIMS and abridged Simpson Scale (Simpson et al., 1979) with videotaping were done at fixed intervals. At the present time, 22 children have been on haloperidol for 6 months, and 11 children for 1 year or more, on doses ranging from 0.5 to 3.0 mg/d.

As for behavioral symptoms, their reduction was maintained at the 6-month followup rating. One week after the discontinuation of haloperidol, ratings of fidgetiness, hyperactivity, stereotypies, withdrawal, and abnormal object relations on the CPRS as well as CGI ratings showed significant increases ($p < .05$, Matched-Pairs Signed Ranks Test).

As for movements, to date four children developed drug-related abnormal movements in this prospective study, as shown in the Table.

In summary, in young children diagnosed as having infantile autism according to DSM-III criteria (axis I), haloperidol, at conservative doses of 0.5 to 3.0 mg/day, yields both clinically and statistically decreases of behavioral symptoms and facilitates learning in our discrimination tasks. This occurs with a bioavailability of ND* or 1.30 to 8.30 ng/ml in serum. On the same dosage, in about 12% of these patients studied prospectively, haloperidol yields worsening of preexisting voluntary abnormal movements or involuntary abnormal movements *de novo;* this occurs while the patient is on drug maintenance (from 3 to 11 months), or as a withdrawal phenomenon. These data were obtained under careful clinical monitoring; drug compliance was excellent.

*ND = < .05 ng/ml

Table

Abnormal Movements Related to Neuroleptic Administration in Four Autistic Children

	Patient No.			
	1	2	3	4
Sex	F	F	F	F
Chronological age* (years/months)	4/2	4/6	3/2	5/2
Haloperidol dosage (mg/day)	1.5	0.5–1.0	3.0	0.5
Treatment schedule**: haloperidol/placebo, in days per week	5/2	5/2	7/0	7/0
Duration of drug administration in months†	3	11	6	6
Onset of movements	On haloperidol	On haloperidol	During withdrawal	On haloperidol
Movements: *de novo* or change in severity or topography of preexisting stereotypies	Preexisting	Preexisting	*de novo*	*de novo*
Duration of movements in months	9	3	< 1	2
Cessation of movements	On placebo§	On haloperidol	On placebo	On placebo

*At the time of enrollment into study.

**5/2 = discontinuous schedule (5 days a week on haloperidol, 2 days on placebo); 7/0 = continuous schedule (7 days a week on haloperidol).

†Prior to onset or change in movements.

§Decrease only.

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A Controlled Study of Methylphenidate in Combination with Academic Instruction

Rachel Gittelman, Ph.D.[1]

The issue whether stimulants are effective in altering children's learning deficits has been, and continues to be, the subject of much controversy (Dykman, 1980). Gittelman-Klein and Klein (1976) compared methylphenidate with a placebo in 61 children of average intelligence who had significant reading lags and no behavior problems. Methylphenidate was found to improve performance on many psychometric tests, but did not affect performance on standardized reading tests. The pattern of results indicated that performance on tasks which require speed of mental processing was improved by the drug, whereas performance on untimed, complex verbal tasks was not. In a further report (Gittelman, 1980), none of the patient characteristics investigated predicted drug effect, as defined by significant improvement in reading performance.

The results of Gittelman-Klein and Klein (1976) might be interpreted to indicate that attention and learning capacity had been enhanced by methylphenidate, but that, in the absence of concurrent special remedial efforts, the children were unable to profit from their better attentional capacity. These results prompted the investigation of the hypothesis that methylphenidate *in combination* with a program of reading instruction would be superior to reading remediation alone in children with reading disorders uncomplicated by other psychiatric difficulties. This study was part of a larger investigation in which three groups were studied: one group received reading remediation with a placebo; a second received academic tutoring and a placebo (without reading instruction); and a third group received reading remediation and methylphenidate.

Method

Subjects

Only children referred by teachers because of poor academic performance were included, pro-

[1]New York State Psychiatric Institute New York, NY 10032.

vided they were not judged to have current behavior disorders. All children received reading remediation which which emphasized the teaching of phonic decoding and encoding skills. In addition, children were randomly assigned to either placebo or methylphenidate, and treated in double-blind fashion.

Results

At the end of the 18-week period, the children were receiving an average of 44.19 mg/d of methylphenidate. The range of daily dosage was from 10 to 60 mg. The children's weight ranged from 24.5 to 78.8 kg, and the mean daily dose was 1.19 mg/kg at the end of treatment (range = .41 to 2.23 mg/kg).

Methylphenidate Effects on Reading Achievement

The scores of the Wide Range Achievement Test (WRAT) and Gray Oral at the end of treatment were not significantly different between the two groups.

On a phonetic reading test, significantly superior performance for the methylphenidate-treated children as compared to the placebo group was found on one of the reading tasks. Trends were found on the Reading Age ($p < .10$) and on the reading of Graded Phonically Complex Words ($p < .06$) in favor of the methylphenidate-treated children. Of the four reading tests of the Stanford Achievement Tests, the Language subtest showed a significant advantage for the methylphenidate group ($p < .02$).

Methylphenidate Effects on Academic Tasks Other Than Reading

The WRAT grade levels of arithmetic and spelling did not differ between the placebo and methylphenidate groups. On the Stanford Achievement Test, the children who were on methylphenidate obtained significantly higher scores than the placebo-treated children on three of the four math measures: Math Computation ($p < .04$), Math Application ($p < .005$), and Total Math ($p < .0003$). In addition, the drug-treated group performed significantly better than the placebo group on the Social Studies subtest of the Stanford Achievement Test ($p < .005$).

Long-Term Effects of Methylphenidate Treatment

The long-term effects of the 4 months of treatment with methylphenidate were examined 2 and 8 months after treatment termination. One of the children received medication or tutoring during these intervals. The two treatment groups obtained indistinguishable scores at both followup points.

Discussion

The inference may be drawn that, among children who receive individual reading assistance consisting of phonetic remediation, the addition of methylphenidate in the doses used induces significant advantages in academic tasks other than reading. The failure to find long-term advantages for the methylphenidate-treated children, when drug effects had been obtained during treatment, suggests that stimulants may not enhance learning. Rather, they may be viewed as improving performance. In contrast with other reports (Swanson & Kinsbourne, 1976), no evidence for state-dependent learning was obtained. Our results indicate that, even at relatively high doses, performance can be significantly improved by methylphenidate. High dosage does not compromise learning (Sprague & Sleator, 1977); whether more drug effects would have been obtained with less medication cannot be addressed.

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Methylphenidate in Adults with Minimal Brain Dysfunction Symptomatology

Jeffrey A. Mattes, M.D.,[1] Lane Boswell, B.A., [2] and Herman Oliver, M.D.[2]

The fate of children with minimal brain dysfunction (MBD) is uncertain. Until recently, it was believed that children outgrow the symptoms of MBD around the time of puberty (Eisenberg, 1966). Recent studies, however, indicate that the outcome of children with MBD is not universally positive. Family (Cantwell, 1975) and followup (Weiss, Minde, Werry, et al., 1971) studies suggest that hyperactive children are at risk for behavioral difficulties, including alcoholism and sociopathy, past puberty; though the symptom of hyperactivity may decrease, distractibility, impulsivity, excitability, low self-esteem, poor academic achievement, and interpersonal difficulties may continue into later life. There are also preliminary data suggesting that stimulant medication may be effective in adult conditions possibly related to childhood MBD (Wood, Reimherr, Wender, & Johnson, 1976; Wender, Reimherr, & Wood, 1981). However, these studies did not include a control group, and so were not able to determine the specificity of drug effect.

The objectives of this study were to evaluate whether methylphenidate (Ritalin), a standard treatment for childhood MBD, is effective in adults with symptoms considered related to MBD, and to evaluate the specificity of drug response. The overall goal was to determine if MBD is a specific diagnostic entity in adulthood with a specific treatment, stimulant medication.

Method

All patients applying to an adult psychiatric outpatient clinic (approximately 3,000 patients during the course of this study) were screened by questionnaires and (for eligible patients) interviewed to determine eligibility. Two groups of patients were identified:

1) an experimental patient group with adult symptoms of MBD (restlessness, poor concentration, emotional lability, and impulsivity) and retrospective diagnoses of childhood MBD (more specifically, MBD with hyperactive symtomatology), and
2) a control group with similar adult symptoms but with no childhood histories of MBD (this controlled for the possibility that methylphenidate is helpful for certain adult symptoms regardless of childhood history).

It was assumed that the control group would manifest adult MBD-like symptomatology as a result of anxiety or depression; however, severe depressives (major depressive episodes of greater than mild severity), schizophrenics, and manic depressives were excluded. All patients were entered into a double-blind, crossover design, and given 3-week trials of methylphenidate (up to 60 mg/day; the actual mean dosage was 48 mg/d) and placebo.

Baseline evaluation included ratings by patients, psychiatrists, and significant others, on MBD-related and other symptomatology. In addition, old school records were obtained, and parents were asked to retrospectively rate the patient's childhood MBD symptomatology. Evaluation of drug effect included ratings by patients, psychiatrists, and significant others.

Results

Final results, with an N of 63 (approximately 30 in each group) are as follows:

The Diagnostic and Statistical Manual-III (DSM-III) diagnoses of the two groups did not differ significantly except, as expected, that the experimental group much more frequently met the criteria for attention deficit disorder, residual type. The most common diagnoses were major depressive disorder (mild in severity; $N = 19$), alcohol abuse ($N = 17$), drug abuse ($N = 16$), borderline personality disorder ($N = 16$), generalized anxiety disorder ($N = 7$), and antisocial personality disorder ($N = 5$).

A number of baseline measures differentiated the two groups. The experimental group (with

[1]Bronx VA Medical Center, Bronx, NY 10468.
[2]Long Island Jewish-Hillside Medical Center, Glen Oaks, NY 11004.

childhood hyperactivity) began drinking heavily at an earlier age (if they drank heavily), had histories of more drug abuse, had missed more time from work, had more conflicts with others, had more childhood antisocial symptoms, and did worse on the aphasia test and the tactual perception test. These differences were in the expected direction and indicate that we were successful in identifying relatively distinct groups.

Unfortunately, however, the groups did not differ in response to medication (the principal analyses were 4-way analyses of variance: Drug x Group x Order x Sex). There was no evidence of overall benefit from methylphenidate in either group, and no tendency for the experimental group to respond better than the control group.

Attempts to identify predictors of drug response were generally unsuccessful. Correlations between the baseline measures and improvement on methylphenidate were, for the most part, nonsignificant; of the few significant correlations with greater improvement, some were in the expected direction (e.g., more drug abuse and more childhood vandalism), but others were in the opposite-than-expected direction (e.g., less temper outbursts and less retrospective parent-rated childhood hyperactivity). Analyses comparing "Improvers" on methylphenidate vs. "Non-Improvers" were also generally unsuccessful in identifying predictors of drug response. In particular, retrospective parent ratings of childhood hyperactivity, reported by Wender et al. (1981), to predict stimulant responsiveness did not predict response in our sample. History of drug abuse (polydrug) was the best predictor of positive methylphenidate response.

Despite these generally negative results, we were impressed that a few patients (about 10 in the total sample) did appear to obtain clinically meaningful benefit from the methylphenidate (but not from placebo); these patients were as likely to come from the control group as from the experimental group. For these patients methylphenidate was recommended clinically following this study, and several of these patients followed this recommendation and continued to benefit from methylphenidate (periodic trials off medication confirmed this benefit). The response to methylphenidate in some of these cases was as dramatic as in the case histories reported by Wood et al. (1976) and Wender et al. (1981).

Discussion

This study failed to find evidence of methylphenidate response among adults with symptomatology suggestive of MBD. No baseline measure, including history of childhood MBD, predicted methylphenidate response. The clinical evidence of response in certain patients was not evident statistically, and is therefore basically anecdotal. It appears that further work should be done to identify predictors of stimulant response among adults with MBD symptomatology.

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Comments and suggestions are invited.

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Psychopharmacology Bulletin
National Institute of Mental Health
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Papers should be written in *third* person, e.g., the investigators found, **Not:** I found, we found. Contents should be *substantive*, not indicative, e.g., the investigator used the gas chromatography method to determine the three molecular structures, **Not:** The author described the method for determining the structure of the drug.

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3. References: References mentioned in the text should appear as full citations in the **References** following the article. We are now using the author-date method of citation, that is, the surname of the author and the year of publication are to be used in the text, i.e.: Smith (1970) compared reaction times . . . or, In a recent study of reaction times (Smith 1970) . . . This method gives readers useful information in the text and enables them to locate the citation easily in the alphabetical reference list at the end of the article.

If a work has two authors, always cite both names every time the reference occurs in the text. If more than two authors, cite all authors the first time the reference occurs; include only the surname of the first author followed by "et al." (not italicized) and the year in subsequent citations of the same reference, i.e.:

Williams, Jones, and Smith (1963) found their data . . . (1st occurrence)

Williams et al. (1963) found their data . . . (2nd occurrence)

4. Abbreviations: Abbreviations should appear in parentheses after the first time they are mentioned in the paper, i.e., Brief Psychiatric Rating Scale (BPRS).

Use generic names in referring to drugs; trade names may be given in parenthesis the first time a drug is mentioned only.

Journal titles should be abbreviated in the *References* according to the National Library of Medicine's Index Medicus.

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Contributions and inquiries should be sent to:

Allen Raskin, Ph.D.
Editor-in-Chief

Lillian Altman
Managing Editor

Psychopharmacology Bulletin
National Institute of Mental Health
5600 Fishers Lane Rm. 10C-14
Rockville, MD 20857

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Psychopharmacology Bulletin

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Book Review

•**Psychotropic Drug Handbook—Third Edition,** is a small book, 6½ x 4½ inches and 198 pages, containing a wealth of information for the physician who prescribes psychoactive medication. For each of the major classes of psychoactive drugs, antipsychotics, antidepressants, hypnotics, etc., there is a general statement describing the symptoms, behaviors, and diagnostic groups for whom the class of drugs is intended, a brief description of the mechanism of action of these drugs, dosage recommendations based on factors such as severity of illness, a section on pharmacokinetics, and a lengthy and complete description of adverse drug effects and how these should be managed.

In addition, the authors, two pharmacologists and a psychiatrist, provide the generic and trade names for marketed drugs in each drug class and the direct cost from the manufacturers for the medication. Other features of the book which I would commend are an initial section on general principles of drug use which discusses issues such as the dangers of polypharmacy, the advantages and disadvantages of divided doses, and the concerns with drug-drug interactions. The back of the book contains sample patient instruction forms which may be given to patients to instruct them in how the medication should be taken and to alert them to possible adverse effects. These are very complete and written in language that would be understandable to most patients.

In sum, I would highly recommend this book to any physician who prescribes psychotropic medication, particularly those in nonpsychiatric fields who would be less likely to be current with research and experience with these drugs than their psychiatric brethren. One note of caution: the book does represent the views of the authors, and others in the field may not always agree with their recommendations for drug use. I was also a little disappointed with the references cited at the back of the book which I felt were skimpy and could be expanded.

The book may be purchased from the publisher, Harvey Whitney Books, 4906 Cooper Road, P.O. Box 42442, Cincinnati, OH 45242. Price: U.S.$9.50, Softbound; 198 pp.

Allen Raskin, Ph.D.
National Institute of Mental Health,
Rockville, MD

Books Received

- **Halluzinogene:** Psychische Grenzzustande in Forschung und Psychotherapie (Hanscarl Leuner, editor) has recently been published by Verlag Hans Huber Publishers, Berne, Switzerland. It is a 458-page, soft-cover book with extensive references. It is in the German language.

• • • •

- **PCP (Phencyclidine): Current and Historical Perspectives.** Ed Domino (ed.), Ann Arbor, MI: NPP Books, P.O. Box 1491, Ann Arbor, MI 48106. Price: $40.00; 527 pp.

• • • •

- **Nutrition and Behavior.** Sanford A. Miller (ed.), Philadelphia, PA: The Franklin Institute Press, Box 2266, Philadelphia, PA 19103. Price: $24.50; 320 pp.

• • • •

- **Serotonin: Current Aspects of Neurochemistry and Function.** (Series: *Advances in Experimental Medicine and Biology*, Vol. 133). Haber, B., Gabay, S., Issidorides, M.R., and Alivisatos, S.G.A. (eds.). New York: Plenum Publishing Corp., 223 Spring Street, New York, NY 10013. Price: $75.00; 798 pp.

• • • •

- **Psychopharmacology of Sleep.** David Wheatley (ed.). New York: Raven Press, 1140 Avenue of the Americas, New York, NY 10036. Price: $29.00; 256 pp.

• • • •

Letter to the Editor:

Sudden Death and Neuroleptics

It has recently come to our attention that the otherwise very excellent column by Dr. Paul Leber in the July 1981 *Psychopharmacology Bulletin* (1) regarding sudden death as a risk of neuroleptic treatment contains an erroneous reference to a recent publication of ours (2). The column indicated us as suggesting that hospitalized chronic schizophrenics may be at *decreased* (emphasis in the column) risk for death compared to the age- and sex-matched general population. The analyses of the article in question were limited to age- and sex-specific mortality rates at two points in time (1970 and 1977) for *hospitalized psychiatric patients only* and indicated a reduction in mortality risk over time in this population. In a subsequent report (3), we compared mortality rates among hospitalized psychiatric patients with general population rates after age adjustment and found consistently elevated mortality among psychiatric patients as compared to the general population. In neither study did we report mortality rates by diagnosis.

We have examined mortality rates (unpublished data) by diagnosis in a large inpatient psychiatric population in comparison to general population rates and have consistently found increased mortality among patients in all age-, sex-, and diagnosis-specific categories. Thus, while it is true that the mortality risk for chronic schizophrenics is the lowest of all diagnostic groups we studied, it is still substantially increased over the risk expected in an age- and sex-matched general population sample.

In a word, chronic schizophrenics in our studies were at *increased* risk for death compared to the age- and sex-matched general population.

We hesitated to make this rather minor point, since the major thrust of the column is excellent and points to important directions for further investigation of rarely occurring potential adverse drug reactions. However, we simultaneously felt that your readership should not be misled by the above misattribution.

Thomas J. Craig, M.D., M.P.H., and
Shang P. Lin, Ph.D.
Information Sciences Division
Rockland Research Institute
Orangeburg, NY 10962

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2. Craig, T.J., and Lin, S.P. Death and deinstitutionalization. *Am. J. Psychiatry*, 138:224-227, 1981.
3. Craig, T.J., and Lin, S.P. Mortality among psychiatric inpatients: Age-adjusted comparison of populations before and after psychotropic drug era. *Arch. Gen. Psychiatry*, 38:935-938, 1981.

Reply to Drs. Craig and Lin

I thank Drs. Craig and Lin for the gracious way in which they draw attention to my mis-interpretation of their findings (1). I assumed, incorrectly, that their calculations of expected 1977 patient deaths employed population based mortality rates for 1970. Their paper clearly states that hospital based rates were used, and I apologize for the confusion created by my incorrect çitation of their work.

The actual findings of Drs. Craig and Lin support the generally held view that populations of chronic psychiatric patients (i.e., subjects likely to have received neuroleptics) have a mortality risk exceeding that of the general population. Thus, their findings do not militate against arguments supporting an etiologic role for neuroleptics in sudden death (the implication I intended in citing their work in my paper).

Paul Leber, M.D.
Food and Drug Administration,
Rockville, MD.
December 7, 1981

1. Craig, T.J., and Lin, S.P. Death and deinstitutionalization. *Am. J. Psychiatry*, 138:224-227, 1981.

Errata

In the January 1982 issue (Vol. 18, No. 1) of the *Bulletin*, pages 95/96 and 97/98 were transposed.

On pages 110 and 111 of Dr. Campbell's article in the January issue (Vol. 18, No. 1) the footnotes should read: *ND = < .50 ng/ml.

Report from a WHO Collaborative Reference Center for the Study of Psychotropic Drugs

Psychopharmacological Research in India

The following is a short resumé of work done in the field of psychopharmacology in India in 1980. The Report was provided by Drs. V.N. Bagadia, V.K. Mundra, and K.M. Dhawale of the Department of Psychiatry, KEM Hospital, Parel, Bombay, India. Their material was obtained from the *Indian Journal of Psychiatry*, and the papers read at the 33d Annual Conference of the Indian Psychiatric Society (IPS) at Ahmedabad and the 11th Annual Conference of the Indian Psychiatric Society—West Zone (IPS—WZ), Mahableshwar, India.

Antidepressant Drugs

A comparative evaluation of dothiepin (Prothiaden) and imipramine in the treatment of severe depression demonstrated no significant differences in efficacy and tolerability between the two drugs (Chaturvedi et al., 1980).

Gurmeet Singh (1980) found a single bedtime dose of Sintamil superior to divided doses in depression. With the single dose there were fewer side effects and greater patient compliance than with the divided doses.

Sharma and Hegde (1980) compared doxepin in a similar fashion and concluded there were no significant differences in effectiveness and incidence of side effects between the two regimes. They caution, however, against using single-dose therapy in a geriatric population.

Sethi and Bhiman (1980) failed to find any significant differences in efficacy of doxepin vs. that of imipramine and amitriptyline. The correlations between serum levels and therapeutic response for each of the three drugs was also poor.

Quadri et al. (1980) found response to d-amphetamine to be an accurate predictor of antidepressant response to the tricyclics imipramine and amitriptyline.

Sethi et al. (1980) have reported four cases of unipolar depressed patients who developed manic features while on antidepressant medication. They consider the age of the patient, metabolic products of the tricyclic antidepressant, and the central monoamine systems as important in the genesis of this effect.

Antipsychotic Drugs

Deo et al. (1980) found fluphenazine decanoate to be an effective treatment in chronic schizophrenics at a dose of 12.5 mg/week.

DeSouza and DeSouza (1980c) compared a weekly vs. biweekly schedule of fluphenazine decanoate. They found that with the weekly schedule, the compliance was superior with fewer side effects and greater therapeutic efficacy.

V.D. Shah et al. (1980) carried out an open clinical trial with penfluridol in chronic schizophrenics and found a good response to this drug in the dosage range of 20-80 mg/week over a period of 3-6 months.

Sharma and Nandkumar (1980) reported results of a double-blind clinical trial of trifluoperazine against trifluoperazine combined with trihexyphenidyl hydrochloride.

Lithium

Venkoba Rao et al. (1980) studied the effects of lithium on the kidney by means of renal function tests and renal biopsy. They failed to find any correlation between renal function and the intensity and duration of lithium therapy. Khandelwal et al. (1980) studied renal function after 1 year of

lithium therapy and also found no significant renal dysfunction.

Sampath et al. (1980a) studied the red blood cell-plasma lithium ratios in manic patients treated with lithium. They found that lithium responders had indeed higher ratios than nonresponders but could not establish a cutoff value to differentiate the two groups. Nataraj and Bhat (1980) did not find any correlation between the saliva serum lithium ratio and clinical response.

Lakdawalla et al. (1980) reported on their experience in treating aggressive behavior and hyperkinetic syndrome with lithium. They have also attempted to draw a correlation between clinical response, dose, and serum lithium levels.

Venkoba Rao and Hariharasubramanian (1980) have reported significant electrocardiographic changes in long-term lithium therapy with serum lithium levels in their patients well within accepted therapeutic range and with no obvious electrolyte disturbance in evidence. They suggested occasional electrocardiogram (ECG) monitoring to forestall impairment of cardiac function.

Hariprasad et al. (1980) have not found lithium to be hepatotoxic, and Sampath et al. (1980c) have failed to note a significant correlation between the patient's insight into his illness and lithium compliance.

Sampath et al. (1980b) presented a single case report of the occurrence of severe neurotoxicity in a young manic patient who had a lithium serum level within the therapeutic range.

Miscellaneous

DeSouza and DeSouza (1980a) reported on the treatment of 1,000 alcoholics with disulfiram. Seventy-six percent of these patients showed a satisfactory response at the end of 6 months. In another paper (1980b), these workers discussed the toxicity of this drug and concluded that it is a safe drug in a dosage of 250 mg/day.

Dhawale et al. (1980) tried disulfiram on 57 patients after giving them an initial challenge with this drug. Using an extensive evaluation scale, they reported a 50% improvement at the end of 6 months.

Khorana (1980) found a fair degree of improvement at the end of the 3d or 4th week in emotionally disturbed children treated with nitrazepam.

Bagadia et al. (1980) tried piracetam vs. placebo in a double-blind fashion in cases of cognitive deficiency resulting from electroconvulsive therapy (ECT). They did not find any statistical difference in the improvement recorded by the two groups.

Kulkarni and Mulay (1980) investigated the value of propanidid vs. thiopentone as an inducing agent in ECT and concluded that propanidid was a better agent because of its faster induction, earlier recovery, and shorter half-life. This would be particularly helpful in rendering better service at public hospitals.

Gada (1980) has reported on three cases of prolonged apnea with succinylcholine during ECT.

Vyavahare and Deo (1980) presented a case report of the value of carbamazepine in brain trauma.

Gautam et al. (1980) tried out an ayurvedic compound (Unmad Bhanjan Ras) in acute psychotic excitement (Vatanmada) in a double-blind fashion. They reported an 85% response recovery rate with the active drug vs. 15% with placebo.

Shah et al. (1980) have carried out a drug surveillance program in psychiatry, the first of its kind in India. They have examined the side effects of drugs, correlation of drug response with socio-demographic factors, clinical characteristics and pharmacological profile of the drug, mechanisms of side effects, and level of patient acceptance. In general, they reported a low incidence and intensity of side effects with the psychoactive drugs. Acceptance was good, and no correlations were found between side effects, socio-demographic factors, and clinical response.

Chakraborty et al. (1980) expressed concern about psychotropic drug use and called on psychiatrists to use minimally effective doses to avoid the danger of turning patients into drug addicts.

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Adverse Drug Reactions—When Is an Adverse Drug Reaction Not an Adverse Drug Reaction?

Paul Leber, M.D.[1]

When is an adverse drug reaction (ADR) not an ADR? Why, when it's not due to drug, of course! When is it not due to drug? When it's due to something else! A child's riddle? Perhaps, but the questions asked are not uncommon ones in both clinical drug research and clinical practice.

The solution to the riddle may or may not be straightforward. When a treatment-emergent event is "characteristic," uncommon in the absence of drug, and occurs in the appropriate temporal relationship to drug administration (i.e., acute dystonia occurring in a young male shortly after beginning on haloperidol), the causal role of the drug seems reasonably established. Moreover, in some circumstances, dechallenge and rechallenge of the patient (if safe and ethical) may provide additional reasons to accept the link between drug administration and the untoward event as causal.

In many circumstances, however, it is not possible to distinguish between events caused by the drug and those contemporaneously associated with drug administration by chance alone. This is especially so when the event in question is a complaint by the patient about an internal subjective state (i.e., mood, feeling, sensation) neither objectively assessable nor readily understood as a predictable pharmacological consequence of the drug's action. Dizziness, headache, light-headedness, nausea, and dysphoric affects are all examples of this sort of alleged ADR. Moreover, when the untoward event may be a sign or symptom of the patient's underlying disorder or condition, the likelihood of making an accurate assessment of the etiology of the event is even more problematic.

It is common, however, to behave as though an event has a known specific cause. The assignment of an etiology to a specific event is often justified on the basis of "clinical judgment." Why clinical judgment should be accepted as a method to certify causality and how it differs from any other "post hoc, ergo propter hoc" argument is unclear. Reflection on the matter will reveal that for all its mystique, clinical judgment is little more than a hunch, an idiosyncratic sentiment. Admittedly, the sentiment (at least in the minds of "good clinicians") is probably close to an intuitively established, experientially based, conditional probability. In the setting of clinical practice, the hunch (read conditional probability estimate) takes the form of the argument that given event "A" there is a likelihood, P(D/A) that the event is caused by drug. What might be used to estimate this likelihood?

Logic alone allows one to argue that nondrug causes of untoward clinical events fall into two conceptually distinct catagories: 1) the pathogenic (i.e., those related to the condition or disease), and 2) the pathoplastic (i.e., those related to each patient's intrinsic characteristics).

If this hypothesis is true, the incidence of clinically observed adverse events will be a function not only of drug, but of both subject- and disease-related factors.

It is, of course, impossible to estimate the relative contributions drug, disease, and population characteristics make to the incidence of untoward clinical events in naturalistic clincial practice settings. Furthermore, criterion variance, observer variance (variability attributable to differences in observer sensitivity to phenomena near their clini-

[1] Food and Drug Administration, Rockville, MD 20857.

NOTE: The opinions expressed here are those of the author, and do not necessarily reflect the views or the policy of the Food and Drug Administration.

cal threshold, technique of elicitation of clinical data, etc.), occasion variance, and duration of observation interval all contribute to uncertainty about the overall event rate, let alone estimation of specific event rates.

Placebo-controlled, double-blind clinical drug trials of parallel design with randomized assignment of subjects to treatment, therefore, offer an unusually valuable opportunity to estimate the drug and nondrug contributions to the incidence of untoward events. Further, when placebo-controlled trials are conducted using the same drug in different diseases or syndromes, comparison of incidence of events between clinical trials may offer some insight into the relative contributions of disease and subject characteristics to the overall event rate (i.e., a distinction between events of pathogenic and pathoplastic origin). As we shall see, however, such inferences must be highly qualified.

One problem in the estimation of adverse event incidence is the variation in event detection and enumeration which arises because of the lack of standardized criteria for the identification of the events themselves (i.e., criterion variance). While one observer's "acute dystonia" is likely to be another's, less concurrence may be expected if "agitation" is the event in question. To some degree, criterion variance can be reduced by employing operational definitions and training raters to the criterion. Clearly, in contrast to clinical practice, this can be done in controlled multicenter clinical trials and, therefore, makes such trials a relatively reliable source of untoward event incidence data. Nevertheless, standardized criteria are only useful for relatively common and previously recognized phenomena. If new or novel untoward events emerge for the first time during trials with a new drug, prospective measures to reduce criterion variance are not possible. Post hoc adjustments of terminology, in cooperation with participating investigators, can be made, however, and may prove helpful. For example, combining several like phenomena under a single heading will reduce the number of distinct adverse events and contribute to the systematic organization and display of the drug's adverse event profile.

Events must also be described in terms of their severity. Again, the excessive criterion and observer variances, characteristic of spontaneous reports from naturalistic sources, may be reduced in large multicenter studies through the use of carefully written protocols and co-training of investigators.

Accurate estimation of adverse event incidence also requires standardized calculation. Defining incidence as the number of individuals experiencing the event divided by the number of individuals exposed seems most consistent with usual statistical practice.

Another problem is the need to account for event duration in event incidence tabulations. To some extent, severity ratings can reflect duration. For example, two headaches of identical intensity but lasting for 1 hour and 3 day , respectively, can be given differential severity gradings. This approach, however, seems somewhat unsatisfactory for it confounds duration and intensity.

While not yet in general use, life table or survivor function methodologies could be applied to this problem. For example, for a given adverse event, it is possible to construct a function which describes the likelihood of experiencing the event (adjusted for dose level or cumulative exposure) as a function of duration of exposure. For the moment, however, it would seem most critical to avoid combining adverse event incidence data obtained from studies of differing duration. While not explicitly stated, incidence figures always imply incidence during a period of specified duration. This point is often overlooked. Indeed, the author has seen instances in which unadjusted incidence figures from clinical trials of different duration have been unwittingly combined.

This brings the author to a major point. The rules for combining adverse event data obtained in clinical trials are essentially those same rules for combining efficacy data. Pooling of data should only be attempted for trials of the same design and duration into which patient samples drawn from the same population have been entered. If event incidence is a function of the disease under treatment (and the author believes that it often is), then it may be misleading to pool data obtained from clinical studies using the same drug in different diseases. Parenthetically, this point is subject to experimental verification.

Again, standard statistical applications of these principles to adverse data analysis are not widely disseminated, but it is theoretically possible to test the appropriateness of pooling adverse event data (i.e., estimate incidence vs. investigator interac-

tions, etc.).

If these points are adhered to, it is possible to arrive at incidence figures for a spectrum of relatively common adverse events reported by or observed in patients participating in placebo-controlled trials. The proportion of subjects experiencing the event on drug and placebo can then be compared. Placebo incidence figures can be used to estimate the spontaneous rate of the event in the population.

This approach was attempted recently in the drafting of the professional product label for a new benzodiazepine anxiolytic drug product, alprazolam (Xanax©, Upjohn, 1981). Both the Food and Drug Administration (FDA) and Upjohn Pharmaceuticals were interested in reporting, in the most accurate manner possible, the "real" incidence of adverse events observed with the drug. Everyone involved in the joint effort recognized that the absolute rate of adverse events is often meaningless. Even when using identical protocols, two "trained" investigators may still detect adverse events at quite dissimilar rates. Our intent was, therefore, not to generate incidence figures for comparison with other drug products, but simply to present the incidence data in the most meaningful way possible.

Consideration was given to the possibility of presenting corrected incidence figures arrived at by either 1) subtracting the placebo incidence rate from the drug incidence rate, or 2) calculating the ratio of the drug incidence to placebo incidence. Both possibilities were rejected because they discarded valuable information. Clearly, it is more meaningful to know that an event was observed 30% of the time among drug recipients and 25% of the time among placebo recipients than it is to learn that the "corrected" incidence is 5% or the "relative incidence" ratio is 1.2.

The final tabulation of adverse events in the alprazolam (Xanax©) label was restricted to those which occurred at a frequency of greater than 1%. The choice of this cutoff point was arbitrary, but it did take into consideration the generally accepted view that typical new drug clinical trials enrolling 500 to 1,000 subjects are unlikely to be reliable at detecting events which occur with a frequency below 5% or so. For example, it is estimated that, in order to be 95% certain of detecting at least one example of a class of events which occur at a true frequency of 1% in the population, at least 300 subjects must be enrolled (Sackett, Haynes, Gent, & Taylor, 1980). It is thus very difficult to get enough events to observe statistically significant differences between drug and placebo rates when absolute rates are low.

As discussed earlier, it is exceedingly difficult to compare adverse reaction severity assessments among investigators. The Xanax© labeling attempts to give some basis for comparative judgment by presenting the incidence of intervention required because of adverse events among drug recipients. (A similar tabulation for placebo was not presented, mainly to avoid further complexity in the labeling.)

It is of interest that the alprazolam vs. placebo incidence figures reveal that it is possible to begin to identify when an ADR is not an ADR.

Whereas drowsiness (a pharmacologically predictable event) among alprazolam recipients was observed at a rate approximately double that of placebo recipients, other observed "traditional" ADRs are subject to different interpretations. For example, light-headedness, confusion, dry mouth, constipation, diarrhea, blurred vision, and weight gain were observed at essentially similar rates in both treatment groups. Depression, headache, insomnia, nervousness, and palpitations occurred at lower frequency among alprazolam-treated subjects. Thus, not only do the ADR incidence figures illustrate the epiphenomena of anxiety, but the comparative incidence figures support the anxiolytic efficacy of alprazolam.

It will be of considerable interest to examine the ADR rates for alprazolam and placebo when and if its efficacy is evaluated in conditions other than anxiety. This may permit some distinction between events commonly reported by subjects in any drug study (pathoplastic phenomena) and those which are more rationally explained as epiphenomena of the condition under treatment (pathogenic phenomena).

Before closing, however, it is critical to emphasize that, at best, untoward event incidence figures are imprecise estimators of true ADR rates. This should be borne in mind when one must assess the claims of commercial sponsors about the relative incidence of ADRs observed with their product and its competitors. Even among studies involving only a single active drug and placebo, it is virtually impossible to decipher the meaning of rates reported from clinical studies

conducted by different investigators, in different patient samples, receiving different amounts of drug in different environmental settings in different historical epochs. Comparisons among two active drug products are even more complicated because, in order to be useful, they must compare patient samples receiving therapeutically equivalent dosages of drug. In short, comparisons of ADR incidence, even if based on data obtained from "poolable" clinical studies of similar design and execution, require cautious interpretation.

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Brief Reports and Reviews—

The Brief Psychiatric Rating Scale for Children[1]

John E. Overall, Ph.D.,[2] and Betty Pfefferbaum, M.D.[2]

Introduction

The Brief Psychiatric Rating Scale for Children (BPRS-C) has been developed to provide a parsimonious description of childhood emotional and behavioral disorders. Beginning with an extended description of the symptom and behavior characteristics associated with some 18 Diagnostic and Statistical Manual-III (DSM-III) categories, the methodology of factor analysis was used to identify clusters of symptoms that define major independent dimensions of difference among the diagnostic groups. Whereas the DSM-III includes specific, and sometimes rather arbitrary, criteria for a large number of childhood diagnoses, it is important to recognize that a relatively few major symptom and behavior dimensions separate those more numerous diagnostic groups. The BPRS-C is designed to characterize individual patients, and to evaluate treatment responses, in terms that are relevant for a variety of different diagnostic classifications. Thus, the multidimensional BPRS-C is considered appropriate for description of major differences among child and adolescent patients and for characterizing such patients according to major syndrome groupings, as well as for the evaluation of treatment responses in longitudinal research designs.

[1]This work was supported in part by USPHS Grant MH-32457-02.
[2]The University of Texas Medical School, Houston, TX 77025.

Requests for reprints should be addressed to: Dr. John E. Overall, Department of Psychiatry and Behavioral Sciences, The University of Texas Medical School, P.O. Box 20708, Houston, TX 77025.

Factor Analysis

In the factor analysis that provided the basis for development of the BPRS-C, the original data consisted of descriptions of hypothetical typical patients in some 18 diagnostic groups recorded on the 63-item Children's Psychiatric Rating Scale (CPRS) (Guy, 1974) by five experienced child and adolescent psychiatrists. The 18 diagnostic groups were selected from the DSM-III in an attempt to represent the range of clinical conditions most likely to be seen in the practice of child psychiatry. The five judges were asked to record what they considered from personal clinical experience to be the most likely level of symptom severity for typical patients in each of the 18 diagnostic groups. This produced $5 \times 18 = 90$ symptom and behavior rating-scale profiles representing a range of different types of childhood disorders. It is relevant to note that the CPRS rating scale on which the diagnostic stereotypes were recorded antedates the newly revised DSM-III, and that it includes symptom and behavior manifestations that span a broad domain of childhood psychopathology. The factors resulting from the analysis are thus conceived to be primary dimensions of symptom and behavior manifestations useful for describing differences among childhood psychiatric disorders in terms other than the specific diagnostic criteria of the DSM-III.

Intercorrelations among the 63 CPRS symptom variables across the $5 \times 18 = 90$ diagnostic profiles provided by the five expert judges were first factor-analyzed by a cluster-oriented powered vector method (Overall & Porterfield, 1962) to identify seven relatively independent

variables which represent distinct domains in the symptom measurement space. An oblique marker variable factor analysis (Overall, 1974) was then accomplished, starting with marker variables identified in the preliminary orthogonal powered vector factor analysis. This resulted in a good oblique simple structure in which most of the 63 variables projected substantially on only one of the seven oblique reference axes. The results from this factor analysis have been reported in some detail elsewhere (Pfefferbaum & Overall, 1981).

The BPRS-C includes three key variables to represent each of the seven empirically-identified factors. Care was exercised to avoid logical redundancies in the selection of symptom variables associated with each factor. That is, the several variables that projected primarily on each factor were inspected, and three variables were chosen for incorporation into the BPRS-C that appear to represent conceptually distinct manifestations of psychopathology that should be susceptible of separate evaluation even though they relate to a single primary factor in the larger symptom domain. In some cases, highly related symptom variables were combined into a single new rating construct for inclusion into the BPRS-C. Each of the seven empirically identified factors is thus represented by three conceptually distinct symptom constructs which appear in consecutive sequence in the BPRS-C format. A facsimili of the 21-item BPRS-C is presented in Figure 1.

BRIEF PSYCHIATRIC RATING SCALE FOR CHILDREN (BPRS-C)

Patient _____

Rater _____

Date _____

		Not Present	Very Mild	Mild	Moderate	Mod. Severe	Severe	Extremely Severe
1.	Uncooperativeness - negative, uncooperative, resistant, difficult to manage.	☐	☐	☐	☐	☐	☐	☐
2.	Hostility - angry or suspicious affect, belligerence, accusations and verbal condemnations of others.	☐	☐	☐	☐	☐	☐	☐
3.	Manipulativeness - lying, cheating, exploitive of others.	☐	☐	☐	☐	☐	☐	☐
4.	Depressive Mood - sad, tearful, depressive demeanor.	☐	☐	☐	☐	☐	☐	☐
5.	Feelings of Inferiority - lacking self-confidence, self-depreciatory, feeling of personal inadequacy.	☐	☐	☐	☐	☐	☐	☐
6.	Suicidal Ideation - thoughts, threats, or attempts of suicide.	☐	☐	☐	☐	☐	☐	☐
7.	Peculiar Fantasies - recurrent, odd, unusual, or autistic ideations	☐	☐	☐	☐	☐	☐	☐
8.	Delusions - ideas of reference, persecutory or grandiose delusions.	☐	☐	☐	☐	☐	☐	☐
9.	Hallucinations - visual, auditory, or other hallucinatory experiences or perceptions.	☐	☐	☐	☐	☐	☐	☐
10.	Hyperactivity - excessive energy expenditure, frequent changes in posture, perpetual motion.	☐	☐	☐	☐	☐	☐	☐
11.	Distractibility - poor concentration, shortened attention span, reactivity to peripheral stimuli.	☐	☐	☐	☐	☐	☐	☐
12.	Speech or Voice Pressure - loud, excessive, or pressured speech.	☐	☐	☐	☐	☐	☐	☐
13.	Underproductive Speech - minimal, sparse inhibited verbal response pattern, or weak low voice.	☐	☐	☐	☐	☐	☐	☐
14.	Emotional Withdrawal - unspontaneous relations to examiner, lack of peer interaction, hypoactivity.	☐	☐	☐	☐	☐	☐	☐
15.	Blunted Affect - deficient emotional expression, blankness, flatness of affect.	☐	☐	☐	☐	☐	☐	☐
16.	Tension - nervousness, fidgetiness, nervous movements of hands or feet.	☐	☐	☐	☐	☐	☐	☐
17.	Anxiety - clinging behavior, separation anxiety, preoccupation with anxiety topics, fears or phobias.	☐	☐	☐	☐	☐	☐	☐
18.	Sleep Difficulties - inability to fall asleep, intermittant awakening, shortened sleep time.	☐	☐	☐	☐	☐	☐	☐
19.	Disorientation - confusion over persons, places or things.	☐	☐	☐	☐	☐	☐	☐
20.	Speech Deviance - inferior level of speech development, underdeveloped vocabulary, mispronunciations.	☐	☐	☐	☐	☐	☐	☐
21.	Stereotypy - rhythmic, repetitive, manneristic movements or posture.	☐	☐	☐	☐	☐	☐	☐

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FIGURE 1

Factor Scoring of the BPRS-C

The 21 symptoms of the BPRS-C are rated for severity on 7-point scales ranging from "not present" to "extremely severe." The items are grouped into subsets of three to form a basis for the scoring of the composite factors which are conceived to represent the major ways in which one type of childhood disorder differs from another. Factor scores are calculated by summing the ratings on the successive subsets of three consecutive scales. This consecutive grouping of items representing each factor was chosen, not only to facilitate factor scoring, but to provide for considered comparison of the relative levels of severity of closely related symptoms. Although the symptoms within each group of three relate to the same factor, it is important to recognize that they may differ in severity in individual patients. Such differences are easier to consider when the symptom constructs are adjacent in the rating scale format. Each symptom should be rated separately, with severity in relation to associated symptoms considered carefully.

The breadth of the domain of psychopathology spanned by the BPRS-C suggests that not all factors are relevant for description of each type of patient. The seven major factor constructs and the symptom rating variables that are combined to define the associated factor scores are presented on the left-hand side of the Table. The DSM-III childhood diagnoses for which each major factor is considered to be particularly relevant are listed on the right. These diagnostic relevances were identified empirically from factor score profiles in the original 63-item data set that was analyzed to define the seven factors.

Brief Psychiatric History for Children

For both research and clinical purposes, it is useful to have selected history and demographic information recorded in a standard format. The relevant background data in the case of children with emotional and behavioral problems include demographic characteristics of the family as well as the child. In our own research, the background data form shown in Figure 2 is used to ensure the systematic recording of at least these minimum

Table

Factor Scoring of the Brief Psychiatric Rating Scale for Children and the Childhood Psychiatric Diagnoses in Which Each Factor Is Represented

Factors	Diagnoses
I. *Behavior Problems*	
Uncooperativeness	Conduct Disorders (all types)
Hostility	Attention Deficit Disorders
Manipulativeness	Oppositional Disorders
	Pervasive Developmental Disorder
	Infantile Autism
	Schizophrenic Disorder
	Major Depression
II. *Depression*	
Depressive Mood	Major Depression
Feelings of Inferiority	Agitated Depression
Suicidal Ideation	Retarded Depression
	Depression (other)
III. *Thinking Disturbance*	
Peculiar Fantasies	Pervasive Developmental Disorder
Delusions	Infantile Autism
Hallucinations	Schizophrenic Disorder
IV. *Psychomotor Excitation*	
Hyperactivity	Attention Deficit Disorder
Distractibility	Pervasive Developmental Disorder
Speech or Voice Pressure	Infantile Autism
	Schizophrenic Disorder
	Agitated Depression
V. *Withdrawal Retardation*	
Underproductive Speech	Avoidant Disorder
Emotional Withdrawal	Schizoid Disorder
Blunted Affect	Elective Mutism
	Retarded Depression
VI. *Anxiety*	
Tension	Separation Anxiety
Anxiety	Overanxious Disorder
Sleep Difficulties	Identity Disorder
	Anorexia Nervosa
	Agitated/Anxious Depression
VII. *Organicity*	
Disorientation	Traumatic Brain Injury
Speech Deviance	Organic Brain Disorder (other)
Stereotypy	Infantile Autism
	Pervasive Developmental Disorder
	Schizophrenic Disorder

items of background information. The Brief Psychiatric History for Children (BPH-C) is printed on the reverse side of the BPRS-C for convenience in use. As the data base grows, numerous interesting questions concerning the relationships of manifest psychopathology in children to background characteristics and family context can be answered. For comparative purposes, it may be useful to have similar information collected in different settings.

It will be noted that a section has been included for recording a tentative DSM-III diagnosis. Although a diagnosis made on the basis of brief contact with the child and parents is at best tentative, such a diagnostic impression is another way of characterizing or describing the patient. The fact that the symptom description recorded on the BPRS-C is not intended to be sufficient for diagnosis is emphasized. In children, as in adults, symptom descriptive classification and diagnosis are two different things. Examination of the phenomenological heterogeneity within major diagnostic categories may lead to eventual refinement of diagnostic concepts. The relationships between manifest psychopathology in children and DSM-III diagnosis should in fact be an interesting focus of future research with the BPRS-C.

Interviews with Parent and Child

The interviews used to obtain information necessary for completing the BPH-C and the BPRS-C rely heavily on the interviewing skills of the experienced clinician, who may be a child psychiatrist, child clinical psychologist, or other mental health professional with training and experience in working with children. The interviewer will be described as a psychiatrist in this discussion simply to avoid redundancy in reciting a list of qualified professionals.

An individualized style which allows the interviewer to maximize rapport is considered most important. Clinical skills unique to the individual can be capitalized on in a flexible semi structured interview. Nevertheless, a format that may help to eliminate extreme variation in the mode of data acquisition will be proposed here. It should allow ample opportunity for assessment in a reasonably short period of time. The use of such flexible, semistructured interviews has been documented to produce adequate reliability and validity in the assessment of children (Graham & Rutter, 1968; Rutter & Graham, 1968) as well as adults (Hedlund & Vieweg, 1980).

An interview with one or both parents, or a guardian, is required. The interviewer is encouraged to begin with open-ended questions regarding the child's presenting emotional and/or behavioral problems. Each identified problem is covered in depth with specific regard to onset, duration, and severity of symptoms. Once each problem has been discussed, a more structured format is used to obtain information for the BPH-C and the various symptoms to be rated on the BPRS-C. Specific queries should relate to activity level, attention span, speech development and possible abnormalities, emotional relationships, mood, suicidal ideation, self-concept, tension or anxiety, vegetative symptoms, fantasies, and delusions or hallucinations. A medication history should also be obtained in the interview with the parent. This interview can usually be completed in 35 minutes.

The interview with the child includes an assessment of the child's perception of his problems and an age appropriate mental status examination. As with the parent interview, this interview begins in an unstructured format allowing the interviewer to establish rapport and observe the child's behavior. Play or other modes of relating may be used depending on the child's age and condition. In the unstructured portion of the interview, the clinician can pay particular attention to activity level, attention span, peculiar mannerisms, speech production and abnormalities, manner of relating, mood, affect, self-concept, preoccupations, tension or anxiety, and delusional thinking or hallucinations that are spontaneously manifest.

During the structured portion of the examination, specific tasks may be assigned to the child in order to ascertain the child's developmental level, attention span, and ability to accept direction. Specific questions regarding friendships, school progress, mood, suicidal ideation, preoccupations, fears, fantasies, and unusual experiences or perceptions should be asked. The nature and severity of any positive findings should be explored in detail.

Since the BPRS-C is intended for research use, it is important to standardize the source of infor-

BRIEF PSYCHIATRIC HISTORY

Patient _____ **Date** _____

Patient Present Age
- ☐ 0-1
- ☐ 2-5
- ☐ 6-10
- ☐ 11-13
- ☐ 14-16
- ☐ 17-19
- ☐ 20 or above

Ethnicity
- ☐ White
- ☐ Black
- ☐ Mexican American
- ☐ Other Minority _____

Sex
- ☐ Male
- ☐ Female

Pregnancy, Delivery, Neonatal
- ☐ Uncomplicated
- ☐ Complicated pregnancy _____
- ☐ Complicated delivery _____
- ☐ Complicated neonatal period _____

School (level)
- ☐ None
- ☐ Preschool
- ☐ Kindergarten
- ☐ Grade 1-3
- ☐ Grade 4-6
- ☐ Grade 7-9
- ☐ Grade 10-12
- ☐ Greater than grade 12

School (performance)
- ☐ Retarded
- ☐ Borderline
- ☐ Average
- ☐ Superior

School (interest)
- ☐ Negative
- ☐ Indifferent
- ☐ Normal interest
- ☐ Excess involvement

Patient living with
- ☐ Mother
- ☐ Father
- ☐ Grandparent(s)
- ☐ Sib(s)
- ☐ Stepparent
- ☐ Step/half sib(s)
- ☐ Other _____

Sibs of Patient
- ☐ None
- ☐ One sib
- ☐ 2-4 sibs
- ☐ More than 4

Birth Order of Patient
- ☐ Oldest
- ☐ Middle
- ☐ Youngest

Family Religious Attitude
- ☐ Atheist
- ☐ Agnostic (doubting)
- ☐ Indifferent
- ☐ Moderate Positive
- ☐ Strong Positive or Fanatic

Present Family Problems
- ☐ Marital conflict
- ☐ Separation or divorce
- ☐ Death of parent(s)
- ☐ Death of sib(s)
- ☐ Criminal victimization
- ☐ Criminal apprehension
- ☐ Work problems
- ☐ Financial problems
- ☐ Alcohol abuse
- ☐ Drug abuse
- ☐ Physical illness
- ☐ Organic CNS involvement
- ☐ Other _____
- ☐ None

Major Patient Problem Areas
- Developmental
- Social interpersonal
- Antisocial behavior
- School
- Poor impulse control
- Alcohol abuse
- Drug abuse
- Sleep problems
- Physical problems
- CNS dysfunction
- Other _____

Father's Education
- Less than high school
- High school graduate
- Some college

Mother's Education
- Less than high school
- High school graduate
- Some college

Duration of This Episode
- ☐ Less than 1 month
- ☐ 1-6 months
- ☐ 6-12 months
- ☐ 1-2 years
- ☐ More than 2 years
- ☐ Life long

Course of Illness
- ☐ Chronic stable
- ☐ Slow decline
- ☐ Recurrent acute episodes
- ☐ First episode

Previous Psychiatric Hospitalization
- ☐ No previous admission
- ☐ Single previous admission
- ☐ Multiple previous admission

Previous Outpatient Psy. Treatment
- ☐ None
- ☐ Non-psychiatric Rx
- ☐ Psychiatrist
- ☐ Psychologist

Nature of Previous Episodes
- ☐ None
- ☐ Same as current
- ☐ Other _____

Family Psychiatric History
- ☐ Father
- ☐ Mother
- ☐ Siblings
- ☐ Other relatives _____

Patient Perception of Problem
- ☐ Mental ☐ Mood
- ☐ Character ☐ Physical
- ☐ Interpersonal adjustment
- ☐ No problem (denial)
- ☐ Other _____

Diagnosis
- ☐ Attention deficit disorder
  - ☐ with hyperactivity
  - ☐ without hyperactivity
- ☐ Conduct disorder
- ☐ Separation anxiety disorder
- ☐ Overanxious disorder
- ☐ Schizoid disorder
- ☐ Avoidant disorder
- ☐ Elective mutism
- ☐ Oppositional disorder
- ☐ Identity disorder
- ☐ Anorexia nervosa
- ☐ Infantile autism
- ☐ Pervasive developmental disorder
- ☐ Schizophrenic disorder
- ☐ Major depression
  - ☐ with psychomotor excitation
  - ☐ with psychomotor retardation
- ☐ Other _____

Past medications _____

Current medications _____

New medications _____

Figure 2

mation used in making the ratings. We recommend that the symptom and behavior ratings be based on direct observation of the child, although important leads derive from the prior interview with the parent. Some research protocols may specifically authorize the use of information derived from other sources; however, in general, the psychopathology should be verified in the interview with the child.

After completing the history and BPRS-C, the psychiatrist is asked to make an initial diagnosis of the child. It is understood that the diagnosis may be based on all information available to the psychiatrist, even though the symptom ratings on the BPRS-C are restricted to information verified in the child interview. The initial diagnosis should be recorded by checking the most appropriate DSM-III diagnosis in the box at the lower right-hand corner of the BPH-C form. In addition to providing past and current medication use, the psychiatrist is also asked to list medications which he intends to start after this initial assessment. If he decides to discontinue any current medications, that should also be noted under new medications.

Conclusion

Much work needs to be done to establish the BPRS-C as a reliable and valid instrument for characterizing childhood psychopathology. We believe that the initial development based on factor analyses of ratings descriptive of a wide range of diagnostic entities has produced an instrument with desirable balance for the representation of different types of psychopathology. Because the BPRS-C is intended for use with different types of patients, it is not expected that all symptoms and behaviors will be present in each patient. Preliminary work has suggested, however, that some of the symptoms, and their combinations into factor scores, are relevant in assessing the severity of psychopathology in each of the major diagnostic groups that were considered in development of the instrument.

Because appropriate evaluation of a new assessment device is best accomplished in the context of ongoing research, we have chosen to present the BPRS-C at this time so that it can be considered in the public domain — an instrument that can be used and evaluated by anyone who has a research program into which it can be usefully integrated. Data for assessing internal consistency reliability and concurrent or predictive validity can also be obtained by the use of the BPRS-C and BPH-C in routine clinical practice, where those data can provide standard descriptive information not inappropriate for retention in the patient's file.

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On the Clinical Response/Serum Level Relationship for Antidepressants II: Lofepramine and Imipramine

John E. Dutt, Ph.D.[1]

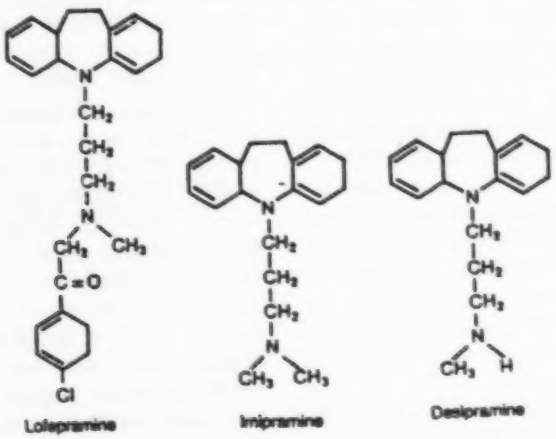
Introduction

In a recent paper by the author (Dutt, 1981), five clinical studies involving amitriptyline (A) and its main metabolite nortriptyline (N) were retrospectively evaluated. In that report, attention was focused on three subgroups of responders, since they tended to be more homogeneous than the full study population. The three groups of responders were:

1) *ALL* responders – Defined as at least a 40% reduction in Hamilton Depression Scale (%Ham− ≥ 40%) scores and a final Ham-D score of 16 or less.
2) Responders for which nortriptyline levels were higher than amitriptyline levels.
3) Responders for which amitriptyline levels were higher than nortriptyline levels.

In the responder groups, there was a pattern of higher correlations between clinical response and steady-state serum level parameters involving both amitriptyline and its metabolite nortriptyline.

The focus of this paper is on two tricyclic antidepressants, imipramine and lofepramine (Eriksoo & Rohte, 1970; Plym Forshell, Siwers, & Tuck, 1976; Siwers, Freyschuss, Hamberger, et al., 1970). These compounds have structures similar to desmethylimipramine (DMI), the main metabolite of each drug. The chemical structures of all three compounds are shown below:



[1]E.M. Laboratories, Inc. (Associate of E. Merck, Darmstadt, Germany), Hawthorne, NY 10532.

Three studies are re-evaluated here—the studies of Gram, Reisby, Ibsen, et al. (1976) and Olivier-Martin, Marzin, Buschsenschutz, et al. (1975) involving imipramine alone, and the double-blind study of D'Elia, Borg, Hermann, et al. (1977) and Siwers, Borg, D'Elia, et al. (1977) comparing lofepramine and imipramine. Individual patient data from a fourth study, the Glassman, Perel, Shostak, et al. (1977) study of imipramine, were unavailable.

In comparing data from different studies, it is essential that there be comparable inclusion criteria, comparable operational definitions of clinical response, uniform handling of data, and a population that can, in fact, respond to the drug (Dutt, 1981; Feighner, Robins, Guze, et al., 1972). Clinical response, which is operationally defined as percent reduction of total depression score from pretreatment to the appropriate posttreatment period, is identified by either percent reduction in Ham-D (Hamilton, 1960) or percent reduction in Cronholm-Ottosson Depression Scale (CODS) (Cronholm & Ottosson, 1960). Depending on the availability of data in each study, the clinical response/steady-state serum level relationship was examined for those most frequently encountered parameters—parent drug (lofepramine or imipramine), the metabolite desmethylimipramine (DMI), metabolite to parent drug ratio (DMI/parent drug), and total serum level (DMI + parent drug).

Additionally, in the double-blind study (D'Elia et al., 1977; Siwers et al., 1977) of imipramine and lofepramine, relationships involving percent norepinephrine (NE) reuptake inhibition after treatment were examined. This latter parameter, which relates to the role of NE as a neurotransmitter in central monoamine nerve terminals, has been found to correlate well in in vivo and in vitro studies with DMI (Plym Forshell, et al., 1976).

The lack of homogeneity of the study populations is again handled by focusing on subgroups of responders, since they tend to be more homogeneous than the full study population. Because responders are used, however, it should not be assumed that significant correlations will inevitably be obtained. The following three groups of responders are considered:

1) *ALL* responders—Defined as at least a 40% reduction in Hamilton Depression Scale (%Ham-D↓ ≥ 40%) scores and a final Ham-D score of 16 or less, or a 40% reduction or more in the CODS scores and a final CODS score of 7 or less.
2) Responders for which the percent of DMI to the parent drug is greater than or equal to 1.
3) Responders for which the percent of DMI to the parent drug is less than 1.

The data are further treated uniformly across studies by imposing the intake criteria of either Ham-D equal or greater to than 18 or CODS equal or greater than 12, and by employing identical statistical methods.

Method

Four studies with adequate sample sizes examined the relationship of clinical response/serum level in patients treated with imipramine for primary depression. These are the studies of Glassman et al. (1977), Gram et al. (1976), Olivier-Martin et al. (1975), and Siwers et al. (1977), which are summarized (Sets 1-4) along with the lofepramine part of the Siwers et al. double-blind study (D'Elia et al., 1977; Siwers et al., 1977) (Set 5). Two desipramine studies (Friedel, Veith, Bloom, & Bielski, 1979; Khalid, Amin, & Ban, 1978) (Sets 6 and 7) are included in Table 1 for discussion purposes. In addition to the Glassman et al. study (1977), there are several other imipramine studies with either insufficient or unavailable data (Malitz & Kanzler, 1969; Moody, Tait, & Todrick, 1967; Muscettola, Goodwin, Potter, et al., 1978; Nagy & Treiber, 1973; Sathananthan, Gershon, Almeida, et al., 1976; Walter, 1971; Watt, Crammer, & Elkes, 1969).

In the four study sets (Nos. 2-5) under evaluation, both in- and outpatients were treated for periods of 3-6 weeks with a fixed dosage except where reductions were necessary because of side effects. With the exception of a subgroup in the Olivier-Martin et al. study (1975), the reported outcome is negative in all four sets. As noted in Table 2, the numbers of nonresponder/nonqualifiers are 12, 9, 6, and 8 in Sets 2-5, respectively. A negative study outcome seems assured, therefore, when the study population contains proportionately large numbers of nonresponder/nonqualifiers. A similar observation was noted with amitriptyline studies (Dutt, 1981).

Table 1

Summary of Significant Results from Seven Study Sets

Study Sets	N	Sample (In/Out Pts)	Treatment Period	Efficacy Parameter	Serum Level: Percent	Serum Level: DMI	Parameters': Percent + DMI	Time of Signif.
1. Imipramine (Glassman et al.)	60	Full In	4 wks	Global (Wk 4)	—	—	Sig[3]	Wk 4
		42[2] In			—	—	0.48**	Wk 4
2. Imipramine (Gram et al.)	24	In	4-5 wks	Tot Ham-D[4] (Endpoint)	—	—	N.S.	Endpoint
3. Imipramine (Olivier-Martin et al.)	24	Full In	3 wks	%Ham-D[5] (Wk 3)	N.S.	N.S.	—	Wk 3
		11[7] In			N.S.	0.70*	Sig[3]	Wk 3
4. Imipramine (Siwers et al.)	19	In/Out	3-5 wks	CODS[6] Amelior. (Wk 3)	—	N.S.	—	Wk 3
					Additional Findings[8] at Wk 3			
					%NE+ vs. DMI ($r = 0.86$***)			
					%NE+ vs. %CODS+ (N.S.)			
5. Lofepramine (Siwers et al.)	20	In/Out	3-5 wks	CODS Amelior. (Wk 3)	N.S.	N.S.	N.S.	Wk. 3
					Additional Findings[8] at Wk 3			
					%NE+ vs. DMI ($r = 0.82$***)			
					%NE+ vs. %CODS+ (N.S.)			
6. Desipramine (Friedel et al.)	25	Out	3 wks	Tot Ham-D (Wk 3)	/	−0.365*	/	Wk 3
7. Desipramine (Khalid et al.)	20	Out	6 wks	Ham-D Amelior. (Wk 4)	/	0.57* ($N = 15$)	/	Wk 4
				(Wk 6)	/	N.S. ($N = 10$)	/	Wk 5

[1]Little or no attention was given to ratios, either D/I or D/L.

[2]Exact figures were not reported.

[3]Significant global response/I + DMI relationships were also found for unipolar nondelusional depressives ($r = 0.435$*, $N = 30$) and bipolar depressives ($r = 0.882$*, $N = 12$).

[4]Total Ham-D was reported to be well correlated with %Ham-D.

[5]Cronholm-Ottosson Depression Scale (CODS).

[6]%NE = % norepinephrine (NE) reuptake inhibition from Week 0.

[7]Endogenous depressives who did not receive concomitant medication.

*, **, and *** denote significance at $p < .05$, .01, and .001 levels, respectively.

Table 2

Responder/Nonresponder Numbers in Relation to Intake Depression Score and Reported Study Outcome in the Seven Study Sets Under Discussion

Study Sets	Median Score at Intake	Responders[1]	Non-Responders	Non-Qualifiers[2]	Reported Outcome
1. Imipramine (Glassman et al.)	— ($N = 60$)	31	29	—	Positive
	— ($N = 42$)[4]	25	17		
2. Imipramine (Gram et al.)	21.5 ($N = 24$)	12	9	3	Negative
3. Imipramine (Olivier-Martin et al.)	27.9[3] ($N = 24$)	15	8	1	Negative
	— ($N = 11$)[4]	10	1	—	Positive
4. Imipramine (Siwers et al.)	18 ($N = 19$)	13	5	1	Negative
5. Lofepramine (Siwers et al.)	16 ($N = 20$)	12	4	4	Negative
6. Desipramine (Friedel et al.)	18[5] ($N = 26$)	16	10	—	Negative (Inverse Relation)
7. Desipramine (Khalid et al.)	24 ($N = 10$)	4	6	—	Negative[6]

[1]Based on the uniform criterion (improvement ≥ 40%; Final score ≤ 16 [Ham-D] or ≤ 7 [CODS]) except study sets #1 and #3. In study sets #1 and #7, the responder/nonresponders are as reported by the authors, and in study #3, according to %Ham-D↓ ≥ 40% only.

[2]A nonqualifier failed to have a score at intake of either Ham-D ≥ 18 or CODS > 12.

[3]Mean score reported by authors.

[4]Subgroup.

[5]As noted in Table 1, a positive outcome was reported for Week 4.

[6]Median score reported by authors.

Statistical analyses included the Spearman correlation coefficient (Conover, 1971) as in Tables 3-5, and the 95% confidence interval for medians as in Figure 1. When statistical significance was found with the Spearman correlation coefficient, this was checked with three additional correlation coefficients:

1) A Pearson based on clinical response as measured by %Ham-D↓ or %CODS↓. These scores were correlated with the logarithms of the serum level parameters.
2) A Spearman based on clinical response as measured by total Ham-D or CODS at treatment endpoint.
3) A Pearson based on clinical response as measured by total Ham-D or CODS at treatment endpoint and logarithms of the serum level parameters.

Table 3

Comparison of Correlation Coefficients Based on Steady-State Serum Levels Averaged over Weeks 4 and 5 for Imipramine Responders from the Gram et al. Study

Time Period	%Ham-D vs. I	%Ham-D vs. D	%Ham-D vs. (I + D)	%Ham-D vs. D/I
Week 3[1,2] ($N = 9$)	+0.62*	N.S.	N.S.	N.S.
Endpoint[1,2] [Wk 4 or 5] ($N = 1$)	+0.84**	N.S.	0.47†	N.S.

[1]Because of a 1-week placebo period, Weeks 3, 4, and 5 correspond to Days 28, 35, and 42, respectively.
[2]For all responders except one, D/I > 1.
†, *, and ** denote significance at $p < .10$, .05, and .01 levels, respectively.

Table 4

Comparison of Correlation Coefficients with Serum Level Parameters at Week 3 for Imipramine Responders from the Olivier-Martin et al. Study

Grouping	%Ham-D vs. I	%Ham-D vs. D	%Ham-D vs. (I + D)	%Ham-D vs. D/I
D/I < 1 ($N = 4$)	0.90*	0.80*	0.90*	N.S.
D/I ≤ 1 ($N = 11$)	N.S.	N.S.	N.S.	N.S.
ALL ($N = 15$)	N.S.	0.41†	0.36†	0.41†
Endog[1] ($N = 10$)	N.S.	0.52†	0.58*	N.S.

[1]Subgroup of endogenous depressive patients identified by Olivier-Martin et al.
† and * denote significance at $p < .10$ and .05 levels, respectively.
(manu. 48)

Table 5

Comparison of Correlation Coefficients with Serum Level Parameters at Week 3 for the Imipramine[1] and Lofepramine[2] Responders from the Siwers et al. Study

Relationships	Lofepramine			Imipramine		
	With Min. Intake (CODS ≥ 12)	Without Min. Intake		With Min. Intake (CODS ≥ 12)	Without Min. Intake	
	Resp. ($N = 12$)	Resp. ($N = 15$)	Total ($N = 20$)	Resp. ($N = 13$)	Resp. ($N = 14$)	Total ($N = 19$)
1. (%NE[1]) vs. (DMI)	0.80**	0.86***	0.89***	0.92***	0.92***	0.92***
2. (%CODS[1]) vs. (DMI)	0.55*	0.24	0.30†	0.20	-0.11	0.8
3. (%NE[1]) vs. (%CODS[1])	0.71**	0.36†	0.33†	0.23	0.26	0.14
4. (%NE[1]) vs. (DMI/Parent Drug)	0.90***	0.86***	0.80***		Not Available	
5. (%CODS[1]) vs. (DMI/Parent Drug)	0.62**	0.40†	0.40*		Not Available	
6. (%CODS[1]) vs. (DMI + Parent Drug)	0.51*	0.25	0.29		Not Available	

[1]Imipramine was not measured in serum.
[2]For all lofepramine responders, D/L ≥ 1.
%NE[1] = %Norepinephrine (NE) reuptake inhibition from baseline (Week 0).
%CODS[1] = %Total Cronholm-Ottosson Depression Score (CODS) reduction from baseline (Week 0).
†, *, **, and *** denote significance at $p < .10$, .05, .01, and .001 levels, respectively.
manu. 49

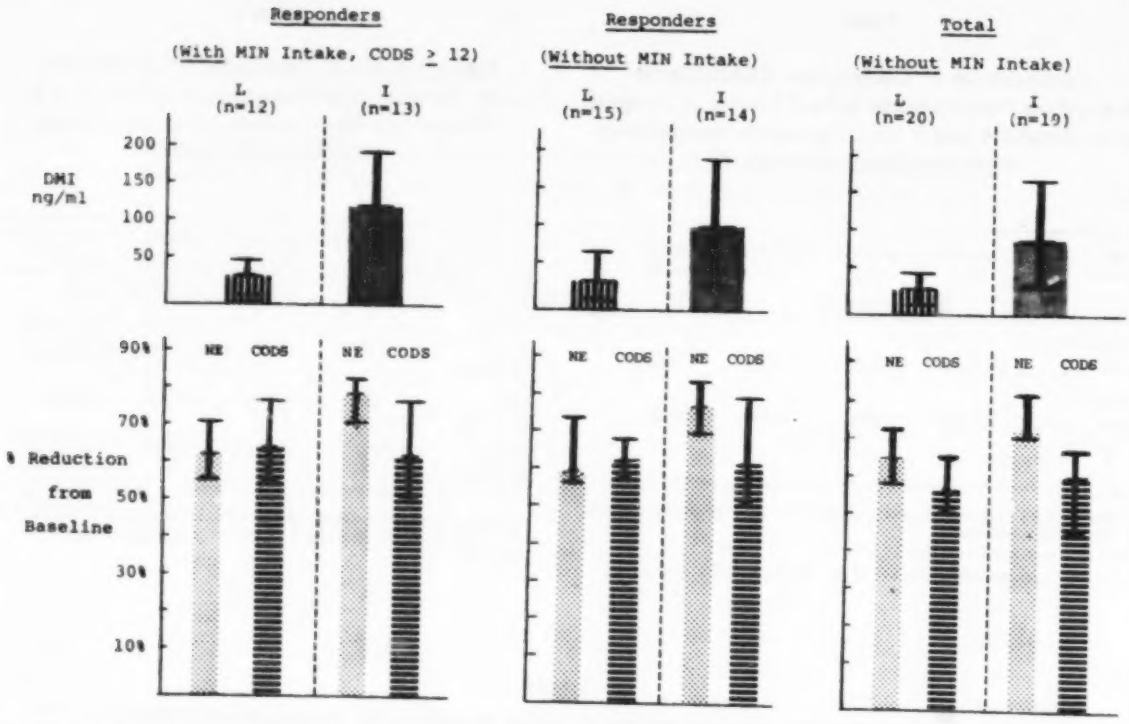


FIGURE 1. Ninety-five percent confidence intervals* for the medians of DMI, percent NE reuptake inhibition, and percent CODS reduction for lofepramine (L) and imipramine (I) treated cases from the Swedish study.

***The 95% confidence intervals here are conservative with confidence probability of at least 95%.**

Results

The Spearman rank correlation coefficients for clinical response as measured by %Ham-D↓ at treatment endpoint, and each of the four serum level parameters I, DMI, I+DMI, and DMI/I are given in Tables 3 and 4, corresponding to Studies No. 2 (Gram et al., 1976) and No. 3 (Olivier-Martin et al., 1975), respectively. For the imipramine and lofepramine responders from the Swedish study (Siwers et al., 1977), a comparison of Spearman correlation coefficients for six relationships, with and without a minimum intake condition of CODS≥12, is available in Table 5. Correlations are primarily computed for ALL responders, without breakdown into DMI/parent drug subgroups, since either imipramine (Swedish study) was not measured or the proportions of (DMI/parent drug < 1) responders were relatively few.

In the Gram et al. study (1976), the authors included a patient at Week 0 with a Ham-D ≥18, or a Ham-D ≥16 and a six-item Ham-D subscore ≥9. In the present evaluation, a patient was included if the average of Ham-D at the beginning (Day 0) and end (Day 7) of the 1-week pretreatment placebo period was >18. Average Ham-D was also used in computing the %Ham-D↓ at Week 3, and at endpoint for Table 3. Because of the 1-week placebo period, Weeks 3, 4, and 5 here correspond to Days 28, 35, and 42, respectively.

In the Olivier-Martin et al. study, unfortunately, intake depression scores are not available so that the number of nonqualifiers with Ham-D ≥18 could not be identified. Because the authors reported a statistically significant correlation for an endogenous depression subgroup of 11 patients, results for responders (10 out of 11) are given in the last row of Table 4.

In Set No. 2 (Gram et al. study), as noted in

Table 3 for ALL responders, statistically significant correlations were found with imipramine (I) serum levels both at Week 3 ($r=0.62^{*}$) and at treatment endpoint ($r=0.84^{**}$). A considerably weaker correlation ($r=0.47$) was found with total serum level. Correlations with D or D/I were not significant.

In Set No. 3 (Olivier-Martin et al. study), for ALL responders weak statistically significant correlations are indicated in Table 4 with D, I+D, and D/I. When ALL responders are subdivided into D/I subgroups, significant correlations are found when D/I <1 with I, D, and I+D but for small sample sizes ($N=4$). For the endogenous depression responders, significance is found with D and (I+D) which is consistent with the findings of Olivier-Martin et al., as noted in Table 1. A computational check reveals that somewhat higher correlations are obtained in this case with Pearson's method, which was used by Olivier-Martin et al., than with the Spearman rank order correlation.

In the Swedish study, in which imipramine (Set No. 4) and lofepramine (Set No. 5) are compared, the invoking of a minimum intake depression score (CODS ≥ 12), as indicated in Table 5, seems to have significant beneficial effects for the lofepramine responders. With the minimum intake requirement, for ALL responders the correlations for all six relationships in Table 5 are statistically significant. In particular, with regard to clinical response and %NE↓, DMI/L was found to correlate better than DMI. Lofepramine itself did not correlate with any parameter.

The picture is less clear for the imipramine responders, partly because imipramine was not measured in serum. Outside of the relationship of DMI and %NE↓, which was found to be significant for both imipramine and lofepramine (Siwers et al., 1977), no significant results were found.

The median values of DMI, %NE↓, and %CODS↓ with their 95% confidence limits for the total groups and ALL responders are given in Figure 1. Within each treatment, the parameter medians for responders are not appreciably different from those of the total group.

The median DMI levels, however, are significantly lower for lofepramine (37-38 ng/ml) than for imipramine (87-114 ng/ml). Correspondingly, the median %NE↓ values are somewhat lower for lofepramine (61-66%) than for imipramine (75-78%). Only minor differences were noted between the two treatments in the medians of %CODS↓, 59-63% for the total groups, and 64-66% for responders. Therefore, the responders achieved a median clinical response of about 65%, with median DMI levels of about 37 ng/ml (lofepramine group) and about 114 ng/ml (imipramine group).

In an effort to tie together clinical response with both %NE↓ and DMI, the difference Δ = (% reduction of CODS − % NE reuptake inhibition) is plotted against DMI for each of the lofepramine and imipramine responders in Figure 2. The graph is divided into four quadrants depending on DMI levels <50 ng/ml or ≥ 50 ng/ml together with values of $\Delta > 0$ or $\Delta \leq 0$.

From Table 6, it is noted that without regard to $\Delta > 0$ or $\Delta \leq 0$, most lofepramine cases had DMI levels ≤ 50 ng/ml, while most imipramine patients had DMI levels ≥ 50 ng/ml, and this difference is statistically significant (Part A). Although the sample sizes are small, there are higher proportions of responders for DMI levels ≥ 50 ng/ml (Part B).

Table 6

Proportions of Patients and Responders with DMI < 50 ng/ml and DMI ≥ 50 ng/ml in the Siwers et al. Study†

A. Proportion of Patients

Drug	< 50 ng/ml	≥ 50 ng/ml
Lofepramine	13	3
Imipramine	5	13

$\chi^2 = 7.89$, significant at $p < .01$

B. Proportion of Responders

Drug	< 50 ng/ml	≥ 50 ng/ml
Lofepramine	69.2% (9/13)	100% (3/3)
Imipramine	60.0% (3/5)	76.9% (10/13)

†All numbers denote the number of patients that satisfied intake CODS ≥ 12.

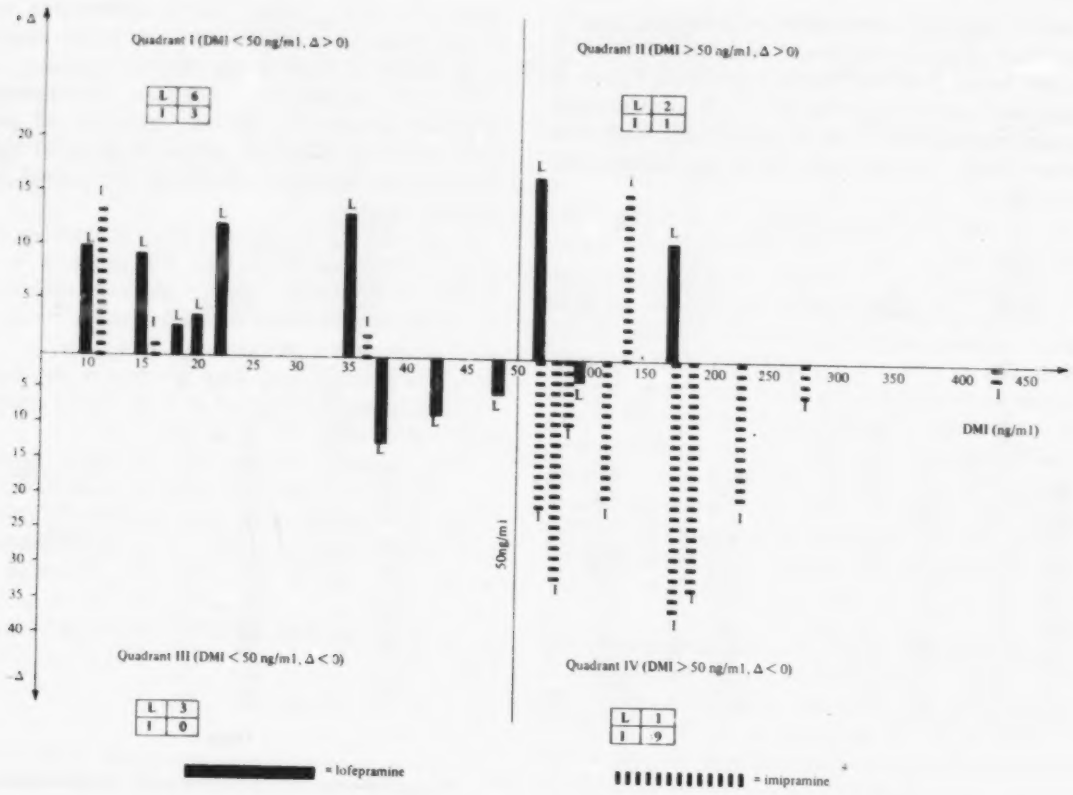


FIGURE 2. The difference Δ (% CODS reduction − % NE reuptake inhibition) as a function of DMI for the responders in the Swedish study.

Table 6 (cont'd.)

C. Proportion of Responders in Quadrants I and IV

Drug	Quadrant I (< 50 ng/ml, Δ < 0)	Quadrant IV (≥ 50 ng/ml, Δ < 0)
Lofepramine	6	1
Imipramine	3	9

$\chi^2 = 4.33$, significant at $p < .05$

D. Proportion of Responders as a Function of Δ

Drug	Δ > 0	Δ > 0
Lofepramine	8	4
Imipramine	4	9

When $\Delta > 0$ or $\Delta \leq 0$ is taken together with DMI levels < 50 ng/ml or ≥ 50 ng/ml, most lofepramine responders are in quadrant I (< 50 ng/ml and $\Delta > 0$) and most imipramine responders are in quadrant IV (≥ 50 ng/ml and $\Delta \leq 0$), and this difference is statistically significant (Part C). In terms of Δ alone, most lofepramine responders have $\Delta > 0$, and most imipramine responders have $\Delta \leq 0$, but the separation is not statistically significant (Part D).

This discrimination property of Δ stems from the fact that the same level of clinical response (median 65%) was achieved with each drug but with substantially lower DMI levels after lofepramine treatment. Since DMI and %NE↓ are highly correlated (Table 5—Relationship 1), and since DMI is lower after lofepramine treatment, %NE↓

is also lower. With the same clinical response but lower %NEI, Δ, therefore, tends to be positive more often with lofepramine treatment. Alternatively, with imipramine treatment, Δ tends to be negative more often.

Discussion

In the past (Asberg & Sjoqvist, 1978; Glassman, Hurwic, & Perel, 1973; Gram, 1977; Hammer, Martens, & Sjoqvist, 1968; Hollister, 1969; Kupfer, Pickar, Himmelhoch, & Detre, 1975; Petit, Spiker, Ruwitch, et al., 1977; Poldinger & Stille, 1969; Preskorn & Biggs, 1978), there has been considerable emphasis on the role and associated problems of serum/plasma/blood-level monitoring of tricyclic antidepressants. The resolving of study inconsistencies that obscure the clinical outcome/serum level relationship, however, is necessary if the value of serum level monitoring is to be realized. The pattern of difficulties, noted previously (Dutt, 1981) in the amitriptyline studies, is also evident in the imipramine studies evaluated here, as may be seen from Table 7.

Table 7

Proportion of Responders/Nonresponders[1] as a Function of Total Serum Levels (DMI + I) or (DMI + L)

Study	R/NR	DMI/Parent < 1		DMI/Parent ≥ 1		ALL	
		< 220	≥ 220	< 220	≥ 220	< 220	≥ 220
Imipramine (Gram et al.)	R	0	1	(5	5)†	(5	6)†
	NR	3	1	3	2	6	3
Imipramine (Olivier-Martin et al.)	R	1	3	4	7	5	10
	NR	—	—	—	—	1	7
Imipramine (Siwers et al.)	R	—	—	—	—	8	6
	NR	—	—	—	—	4	1
Lofepramine (Siwers et al.)	R	0	0	(12	0)*	(12	0)*
	NR	1	0	3	0	4	0

[1]The nonqualifiers are not included.
†Confirmed significant clinical response/serum level relationship with only the parameter I.
*Confirmed significant clinical response/serum level relationships with parameters DMI, DMI/L, and DMI + L.

In the three imipramine study sets, it was only possible to obtain confirmed statistical significance with one parameter in the Gram et al. study. The numbers of responders with total serum level ≥ 220 ng/ml in those three studies are relatively large, viz., 6, 10, and 6. On the other hand, with the lofepramine responders, confirmed statistical significance occurred in three parameters: DMI, DMI/L, and (DMI + L), while for any responder the total serum level did not exceed 220 ng/ml. These results are consistent with what was previously reported for amitriptyline studies. In other words, there is a greater likelihood of confirmed significant results when the number of responders for which total serum level ≥ 220 ng/ml is small (Dutt, 1981).

With regard to the two desipramine studies (Friedel et al., 1979; Khalid et al., 1978) summarized in Tables 1 and 2, again, the large numbers of nonresponders present a problem. In the Friedel et al. (1979) study, an inverse relationship ($r = -.365$) between clinical response and DMI and hence a negative outcome was reported for the full study group. Dropping the large number (10) of nonresponders and focusing on responders (10) with 50 ng/ml < DMI < 200 ng/ml, a positive outcome is possible. In the Khalid et al. (1978) study, there are too few responders for analysis.

The analyses with the lofepramine responders revealed a number of interesting findings. For example, the use of the somewhat stringent intake criterion (CODS ≥ 12) appeared to substantially improve the likelihood of finding statistically significant clinical response/serum level relationships. It is recalled from Table 5 that all six relationships were significant. In addition, the ratio DMI/L was found to correlate better than DMI. It is not clear why this occurred. All lofepramine responders had DMI/L > 1.

The relationship of NE reuptake inhibition and clinical response needs to be explored further in patients that respond to other antidepressant drugs. The finding that most lofepramine responders have Δ > 0 while most imipramine responders have Δ < 0 is certainly interesting. It would be useful to see if Δ, as a function of metabolite serum levels, has a discriminating role with other tricyclics. On the other hand, as is always the case, it would be desirable to see if these findings could be duplicated in additional

studies with lofepramine and imipramine.

This evaluation suggests again the desirability of having large numbers of patients who respond to the drug. Stringent intake criteria for all patients and subsequent dosage adjustment for those patients with total serum levels ≥ 220 ng/ml can increase the likelihood of predicting clinical outcome from serum levels. Hopefully, with these and other measures to improve sample homogeneity, there will be a greater body of consistent study results for tricyclic antidepressants.

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Models of Cognitive Impairment: Cognitive Changes in Depression[1]

Herbert Weingartner, Ph.D.,[2] and Edward Silberman, M.D.[2]

Introduction

Cognitive dysfunctions are an integral aspect of the behaviors evident in depression. One of the most obvious clinical expressions of depression is reflected in how these patients experience and describe themselves, significant others, and their environment. These subjective as well as observed cognitive changes can appear as alterations in the perception, organization, interpretation, and meaning of a large variety of events or stimuli. Past events, stimuli in the present, as well as future events are appreciated in qualitatively different ways from the nondepressed state. Depressed patients also experience and demonstrate difficulties in concentration, attention, memory, and other aspects of information processing. That is, while depressed, there appear not only qualitative changes in cognition, but quantitative changes as well, and the efficiency or effectiveness of information processing is compromised in the depressed state. The clinical and experimental studies reviewed here demonstrate that these qualitative and quantitative changes in cognition are complex and highly variable in form. The purpose of this review is to outline and structure what we have learned about cognition in depression. Some of these findings can be clinically useful. They also may teach us some things about the psychobiology of mood and cognition. Finally, we consider some of the questions that remain to be answered and propose some directions for further study and research.

A remarkable diversity of studies has been completed to date. Some of the findings come from clinical studies using clinical assessment tools. In other studies, patient populations have been examined using laboratory based methods and procedures. Still other studies have tested unimpaired subjects, manipulated their mood, and then examined changes in cognition. Methods have varied with respect to the types of subjects studied, the definition of depression, the theoretical framework that has been used to interpret cognitive responses, and the nature of the cognitive response that has been used as the target behavior.

The structure of this review is as follows. The findings that describe changes in the *form* of cognition (qualitative changes) and the *effectiveness* of those cognitive processes (quantitative changes) in depression will be reviewed separately. Some of these cognitive changes will then be compared to the changes in cognition apparent in other disorders, particularly those evident in early-stage dementia. An underlying theme throughout the review is whether there are distinctive features to the cognitive changes in depression that differentiate them from forms of cognitive impairment associated with other states. We then consider

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[2]Laboratory of Psychology and Psychopathology, National Institute of Mental Health, Bethesda, MD 20205.

why it is difficult to integrate the available data base on cognition in depression. A framework is provided that may be useful both in integrating aspects of cognitive processes apparent in depression and in providing methods and interpretative schemes for further study. Finally, we describe some of the major questions that remain to be answered by such future study.

Qualitative Changes in Cognition in Depression

Three types of findings have supported the contention that depressed patients think about, interpret, and remember events in a manner that is different from processes apparent in the undepressed state. Psychodynamic formulations of depression have been one basis of these findings. Cognition in depression is considered in terms of a recapitulation of processing strategies used during some early developmental stage. Observed cognitive behaviors in depression, such as helplessness, passivity, and dependence, are then interpreted within a context of the consequences of a developmental history, and disruptions in stages of that history. This view of cognitive processing in depression has been reformulated on the basis of versions of experimentally based learning theories (operant theories, behavior modeling theories, and cognitive versions of behaviorism) as developed within experimental psychology, and have served as an important basis for describing the qualitative changes in cognition in depression. A second basis for describing qualitative changes comes from studies in which mood is manipulated, using a variety of laboratory procedures. Here the strategy is to model or mimic the types of mood changes evident in depression and then characterize related changes in cognition. A third source of data has been generated from studies that have used information processing models to examine alterations in the form of cognition in depression. In these studies, mood-state is viewed as a form of context for encoding processes and retrieval processes. In other terms, mood states are defined in terms of their stimulus properties, in much the same way that a drug manipulation is associated with unique stimulus properties. A mood-state then serves to bias the form of cognitive processing in a unique manner.

During the past two decades there have appeared a number of different kinds of studies, each demonstrating that life events, a particular developmental history, and other factors result in a pattern of cognitive behaviors which are then related, or determine the experience of depression (Brown, Sklair, Harris, & Burley, 1973; Forrest, Fraser, & Priest, 1965; Jacobs, Prusoff, & Paykel, 1967; Paykel, 1975; Paykel, Myers, Drenelt, et al., 1969). In these studies, it would appear that depressed patients think about past, present, and future events differently from what is apparent in the undepressed state. In some instances, these studies have served as a basis for formulations of cognitively focused theories that would describe the etiology of depression and what maintains depressive symptoms. For example, Beck has conceptualized the cognitive aspects of depression as reflecting a negative view of self, lowered self-esteem and decreased motivation, and related specific and systematic distortions that serve as a primary integrative theme for depressed cognition (Beck, 1967, 1971, 1974). Beck has argued that dysfunctional cognitions are, in fact, at the heart of what constitutes the experience of being depressed. Cognitively, depressed patients overgeneralize, selectively abstract information, are susceptible to some arbitrary forms of interference and, most important, minimize positive consequences and maximize negative consequences. These last issues or observations have been used by Seligman (1971) in his reformulation of Beck's theory. This has taken the form of the "learned helplessness" theory in depression. The phenomenon has been produced in animals (Maier & Seligman, 1976) and manipulated or modeled in man as well as used to describe cognition in depressed subjects. Depression is viewed as the result of learned helplessness or the expectation that outcome or consequences are response-independent. Feelings of helplessness are considered the focal behavior in depression and are operationalized as expecting consequences to be independent of what one does in some situation (Abramson, Seligman, & Teasdale, 1968; Seligman, 1971, 1975). In depression, patients expect unfavorable events to occur, feel they have no control over those negative consequences and, as a result, demonstrate passivity and a negative cognitive set. Another type of

cognitive-theoretical formulation that is superficially similar to a learned helplessness description deals with internal vs. external loci of control and how these are altered in the depressed state (Hiroto, 1974). Such a theoretical position has been used to interpret attributing failure to self, and self-blame for some outcomes as particularly characteristic of depressed patients (Klein & Seligman, 1976; Rizley, 1978).

Another form of cognitive theory that seems to account for the uniqueness of cognitive processes in depression deals with perceived competence or ability to effectively cope with the environment. Lewinsohn has described the cognitive experience of depression in terms of impairments in social competence. Depressed patients are less interpersonally and socially skilled (Lewinsohn, Mischel, Chaplain, & Barton, 1980), and, therefore, less interpersonally effective. Yet another theory about the nature of the qualitative changes in depressive cognition has been suggested by Bandura in terms of the notion of self-efficacy. He argues that individuals have cognitive schemas that involve their conviction about whether they can successfully execute some behavior that is required of them, one that would produce some desired outcome. Expectations of personal mastery effects both the initiation and persistence of such coping behaviors. The strength of an individual's conviction about his own effectiveness will determine how much effort he will extend and how long he will persist in the face of obstacles and adverse experiences. The stronger the perceived self-efficacy, the more active will be his efforts in dealing with a stressful situation. Successful performance encourages a positive view of self and, in turn, the more positive the view, the more likely is the individual to attempt further tasks and be successful. Self-efficacy then becomes a concept that ties an individual's view of himself with his ability to master situations, and both of these determine his perception of his previous and recent history of success and failure.

These behaviorally oriented theories of depression formulated by Lewinsohn, Seligman, Bandura, and others have spurred a good deal of interest, empirical study, and further theoretical refinement and reformulation (Abramson et al., 1968; Huesmann, 1978; Seligman, 1978). Such theories have also been criticized as too simplistic and inexact descriptions of cognitive processes, since learned helplessness models predict patterns of cognitive symptoms that do not in fact occur in depression (Buchwald, Coyne, & Cole, 1978; Costello, 1978). In addition, much of the theorizing and empirical findings in support of these cognitive theories of depression assume that a manipulation of dysphoric mood in an unimpaired subject is like depression in a mood-disorder patient. Clearly, this is an oversimplification (Wortman & Dintzer, 1978). In fact, most of the empirical studies of these cognitive models of depression have been accomplished in laboratory tests in unimpaired subjects rather than in depressed patients. For example, learned helplessness has been manipulated by altering outcome, e.g., success or failure on skill tasks, which then produces impairments in performance, cognitive and motivational changes, and alterations in the expectation of contingent reinforcement (Abramson et al., 1968). What a subject attends to after some manipulation may also be a consequence of laboratory-based failure manipulations, rather than an alteration of expectations of success and related changes in mood (Coyne, Metalsky, & Lavelle, 1980). That is, manipulation of success or failure on some complex task may primarily alter focus of attention and only in a secondary way alter expectation of success or mood. In general, however, the cognitive behaviors that follow the experience of failure have been interpreted as learned helplessness or loss of perceived competence, and these cognitive changes appear to mimic depression. Critics of these behavioral-cognitive theories point out some of their shortcomings, including the circularity in some of the reasoning. Although the theories may be descriptively useful, they nevertheless explain little about the nature of the cognitive experience of depression (Diener & Dweck, 1978). Furthermore, the major type of manipulation that has been used as an empirical basis for learned helplessness has also served to account for anxiety (Lucas, 1952), stress (Lazarus, Deese, & Osler, 1952), frustration (Lawson & Marx, 1958), and schizophrenia (Garmezy, 1966). It is also not clear from such theories why a negative cognitive set can be induced in some people and not others. Nor do these theorists specify the presence or role of these altered forms of cognitive processes in the various stages that mark the development and mainte-

nance of depression (Blaney, 1977).

The above theories and related methods and procedures used to test them have also been used to generate strategies for cognitive manipulations in altering depressive behaviors, or forms of cognitive therapies. These cognitive therapies have been designed to reverse or alter the mediational styles and behaviors that presumably maintain depression. That is, they are formulated and used to alter the way depressed individuals think about themselves, their competence, and their expectations of success or failure. Consistent with behavioral views of psychopathology, where symptoms are the targets of change, cognitive therapies have been used to change the thinking and cognition of depressed patients. If cognitive changes are produced, it is expected to be reflected in alterations in behavior, thereby effecting changes in depression. Personal mastery initiation and persistence training in coping behaviors are just some of the manipulations that have been used to alter mood in depressed patients. These techniques have also included attentional redeployment (Coyne et al., 1980), and direct cognitive manipulations of self-esteem (Coleman, 1975; Raps, Reinhard, & Seligman, 1980), as well as manipulations of reinforcing consequences that would be expected to alter cognitive behaviors related to depression.

All of these behaviorally oriented theories and studies imply that cognition is qualitatively altered in the depressed state. This has not been tested directly in an effective manner. That is, relatively little research has been explicitly directed at characterizing empirically, qualitative, mood-state specific encoding of events, how information is organized, and how memory for past and recent events is scanned and recalled. Instead, it has been anecdotal, clinical data which has served as a basis for describing changes in how depressed patients interpret information about self, others, their environment, and their past histories. Some of these inferred qualitative changes in cognition have, in fact, been the starting point of some of the cognitive theories of depression as described by Beck (1967, 1971, 1974), Seligman (1971, 1975, 1978), Lewinsohn, Mischel, and Chaplain (1980), and Bandura (1977). Despite extensive laboratory studies in which mood is manipulated in unimpaired subjects or altered by affective illness, there is, nevertheless, little clear and direct evidence that cognition is qualitatively altered in depression. Some studies have shown that when depressed, people recall qualitatively different past events than those that they remember under normal mood-state conditions (Lishman, 1972). That is, positively charged past events are less likely to be remembered when depressed and, instead, depressed patients selectively recall negatively charged events. There are similar findings that have been reported on the basis of laboratory studies of mood and its effects on selective recall of previously processed events. For example, in laboratory studies in which mood is manipulated by a success-failure condition (on a skill task), there appears to be selective and biased recall of positive and negative feedback that differentiates depressed patients from control subjects (Nelson & Craighead, 1977). Depressed patients selectively underestimate the frequency of positive reinforcement even while accurate in estimating the frequency of contingent negative consequences received during the performance of some skill task. A similar type of finding has been obtained in tests of depressed subjects in estimating correct responses on a pseudo-social intelligence task (Wener & Rehm, 1975). Unimpaired subjects who are induced into experiencing a depressive-like mood, as opposed to experiencing a happy mood, required a longer time to retrieve pleasant memories when happy and demonstrate decreased response latencies in recalling unpleasant memories when happy (Teasdale & Fogarty, 1979). All of these studies suggest that mood-states bias the accessibility and retrieval of information already in memory (Weingartner, Miller, & Murphy, 1977). Depressed patients, in recalling recent biographical (episodic) events, are far less likely to recall positively valent material than either neutral or negatively charged information (Breslow, Kocis, & Belkin, 1981). There are also aspects of the cognitive styles of depressed patients that are employed in recalling recent events, that differentiate them from subjects with normal mood. The depressed patient is far more likely to be preoccupied with, or attend to, past events than events that occur either in the present, recent past, or future (Wyrick & Wyrick, 1977). Other studies have been designed to examine the perception of recent life-stress events and have found that depressed patients report

more stressful recent events than controls (Brown et al., 1973; Forrest et al., 1965; Hammen & Cochran, 1981; Jacobs et al., 1967; Paykel et al., 1969), although this may not relate to the actual occurrence of more frequent prior life stresses. The depression-related cognitive style, and changes in how past and present events are scanned and interpreted, are also reflected in alterations in self-schemata or perception of self. These self-schemata changes then also result in alterations in how information about self is organized in the depressed mood-state. Together, these findings seem to all suggest that the cognitive styles of depressed patients are, in fact, different from those apparent under normal mood-state conditions. The kinds of attributes of stimuli that are attended to, the types of past events, the valence of those past events, all seem altered in depression. These qualitative changes may also play a role in defining the nature of the quantitative changes that are apparent in depression. What is less clear is whether such qualitative cognitive changes are also evident in patients even after they have recovered from their depression.

The other form of empirical and theoretical evidence that suggests that cognitive process in depression is qualitatively different from that used normally, comes from studies of state-dependent or dissociative learning under mood-altered condition. State-dependent or dissociative studies were first accomplished in animal learning paradigms, comparing performance under a variety of acquisition and retrieval conditions. These studies have shown that the stimulus properties of drugs can serve as discriminative stimuli biasing the type of response that is elicited from some repertoire (Overton, 1968, 1971). Animals taught a response in a drugged state seemed to "forget" that response in the undrugged state. These dissociative effects have been attributed to discriminative stimulus properties of the drug, where responses are uniquely tied to stimuli represented by some drug-altered state. Similar effects have been demonstrated in drug-state-dependent learning studies in man (Goodwin, Powell, & Bremer, 1969; Weingartner, 1977; Weingartner, Adefris, Eich, & Murphy, 1976). On the bases of these studies in man, it has been possible to demonstrate that memory dissociations occur when events are poorly processed, and when recall is attempted by freely remembering information (Eich, Weingartner, Stillman, & Gillin, 1975; Weingartner, 1977). A number of studies have also demonstrated that the depressed mood state represents a state much like a drug state. It acts as a form of an informational context that, much like a drug, biases or determines how information is processed, encoded, and organized in memory. For example, when a patient in a depressed mood tries to remember previously processed events under normal mood conditions, there appears a form of dissociative learning and memory which is very much like that evident under drug-altered conditions. Sequences of events, such as past biographical experiences, are less likely to be remembered under a disparate mood condition, especially under free remembering conditions, but not when recall is attempted in the presence of strong cues that would ordinarily aid recall. Events that were stored while depressed are less likely to be recovered under normal mood-state conditions, and those events that were stored under normal mood-state conditions are less accessible in the depressed state (Weingartner et al., 1977; Weingartner, Murphy, & Stillman, 1978). That mood states can serve to produce dissociations which are mainly apparent in freely remembering information has been used as evidence for a change in how events are encoded or interpreted in the depressed state.

In summary, a variety of types of convergent findings have been used to infer that depressed patients process events qualitatively differently from how information is processed under undepressed mood-state conditions. However, what is lacking is direct evidence or measurement of cognitive processes themselves, rather than inferences drawn from subjects, levels of learning and memory. The types of findings that suggest qualitative changes in cognition in depression relate to the sorts of biographical experiences that come to mind, recall of reinforcing consequences (success and failure), expectations of future reinforcement, how events are organized, information about the self, and how events are encoded and tied to some mood context. These factors all serve to differentiate the cognitive processes in depression from those evident under normal mood conditions.

Quantitative Changes in Cognition

Depressed patients frequently complain of impairments in cognition. These are frequently verbalized as problems in attention, concentration, memory, and learning, and can be reflected in difficulties in solving problems, persisting on some cognitive tasks, thinking clearly, and distractability. Any or all of these experienced cognitive impairments can be evident on clinical examination, although both their expression and severity may vary widely as a function of the severity of depression and also perhaps the type of depression. In fact, the cognitive dysfunction may be severe enough so that it can resemble the profound cognitive impairments evident in progressive dementia patients.

Although there are considerable anecdotal data describing changes in the effectiveness of cognitive processes in depression, relatively little systematic empirical research has been accomplished to date. Most studies confirm the clinical description of a cognitive impairment in depression, but have not, as yet, defined a) the structure and specificity of these cognitive changes, b) the mechanisms that determine them, and c) the features of cognition during depression that distinguish them from the cognitive dysfunctions associated with other syndromes.

Most of the empirical tests or studies of quantitative changes in cognition apparent in depression have used standard psychometric or laboratory procedures to document and quantify the presence of a deficit (Stromgren, 1977). These procedures have primarily focused on attention, or memory and learning, although rarely together in the same study. Mediation or rehearsal processes that might account for changes in attention, learning, and memory have not been studied systematically. In large part, this is due to the fact that while there are many "ready-made" pretested procedures for measuring attention, learning, and memory, it is much more difficult to measure changes in underlying mediational or rehearsal processes that are hypothesized to determine the effectiveness of various types of cognitive operations.

Investigators have used one of three types of models of information processing as a basis for exploring the cognitive impairment in depression. Each of these models includes methods of approach as well as interpretative schemes for defining or describing cognitive findings. Most of the information processing studies in depression have implicitly or explicitly used some version of a stage theory or model of information processing (Atkinson & Shiffrin, 1968). These theories assume that information processing occurs in discrete stages in which the control or operating processes are different for each stage in processing and storing events, and the nature of the trace of experience is different for each stage of information processing. Aspects of attention, short- and long-term memory, retention, and retrieval are considered to be determined by different psychobiological mechanisms. Any impairment, in any single stage of information processing, would result in a failure to adequately record or recall ongoing events. This model has been used in several studies describing cognitive changes in depression. An alternative theoretical view of how information processing succeeds or fails considers learning, memory retention, and retrieval along a single continuum (Craik & Lockhardt, 1972; Craik & Tulving, 1975). This single process (or "levels of processing") framework for describing information processing has also begun to be used to describe cognitive changes in depression (Weingartner, Cohen, Martello, & Gerdt, 1981). The assumptions in this theoretical approach are very different from stage theory descriptions of information processing. Acquisition, retention, and retrieval are defined not by different mechanisms. Instead, the completeness of encoding or processing at the time of acquisition, and the relationship between retrieval context and encoding context at the time of acquisition, define the probability that learning has taken place and remembering is possible. In many instances it has been possible to show that memory fails because encoding operations have been weak or incomplete. A third type of theoretical model used to explore the nature of cognition in depression considers the events that follow information processing to be important in defining whether or not a trace of experience, a memory, is established in some relatively permanent form. The basic notion is that biological events that succeed acquisition will determine the consolidation of trace events in memory (McGaugh, 1966; McGaugh, Zornetzer, Gold, & Landfield, 1972). This model has been used almost exclusively in studies of the biology of

animal learning and only more recently in studies of information processing in man (Parker, Birnbaum, Weingartner, et al., 1980; Weingartner, Hall, Murphy, & Weinstein, 1976).

A number of studies have demonstrated a relationship between the intensity or severity of depression and the extent of cognitive impairment (e.g., memory) that is present (Harness, Bental, & Carmon, 1977). In some studies, the severity of depression is directly related to impairments in long-term memory (Henry, Weingartner, Murphy, & Murphy, 1973), while other studies have shown this relationship with short-term memory functions (Sternberg & Jarvik, 1976). This difference may be one of semantics, or type of descriptors used to measure such cognitive impairments. By contrast to the above studies, it appears in some reports that the cognitive dysfunction in depression is a highly generalized nonspecific impairment in memory (Stromgren, 1977). Other interpretations of cognitive findings have suggested that memory impairment that is evident in depressed patients may simply be a function of the depressed individual using a more conservative response strategy, one that underestimates what the patient has learned and could potentially remember (Miller, 1975). It would appear that at least some aspects of the cognitive failures evident in depression are accounted for by retrieval failures in the form of increased reaction time, response inhibition, conservative response biases, or output failures, rather than an inability to attend to and acquire new information (Hale & Strickland, 1976; Harness et al., 1977).

A number of studies have also demonstrated that depressed patients demonstrate types of cognitive "blurring" in the form of illogical thinking—failures to accomplish detailed, analytic thinking—and also demonstrate difficulties abstracting, forming concepts, and organizing their experience. These same types of cognitive failures may be reflected in the form of inaffective mediational processes. It is plausible that memory changes that are apparent in depressed patients are a direct result of disruptions in those cognitive processes involved in the encoding of information at the time of acquisition. This may be reflected in the depressed patient being unable to perceive or use structure inherent to some informational input, thereby failing to acquire new information which is then ultimately reflected in failures in recall. In fact, some direct evidence substantiates the hypothesis of impaired analytic cognition, leading to memory changes. One form of this evidence is that depressed patients cluster related events less completely than unimpaired controls (Koh, Kayton, & Berry, 1973; Russell & Beekhuis, 1976). Other findings have demonstrated that depressed patients are less able to process and remember unrelated events, but are indistinguishable from controls in processing and recalling related information (Weingartner et al., 1981a).

Another category of investigation which has yielded information about quantitative cognitive changes in depression is that of neuropsychological testing. The Halstead-Reitan battery, for example, has been reported to show evidence of "right-hemisphere impairment" in two studies of depressed populations (Flor-Henry, 1979; Goldstein, Filskow, Weaver, & Ives, 1977). Such a conclusion is inferred from a pattern of test results characterized by relatively greater deficits in performance of spatial or holistic tasks compared to verbal, numerical, or sequential tasks. When tested in the remitted state, however, depressives have not shown deficits or lateralizing signs on the Halstead-Reitan battery (Small, Small, Milstein, & Moore, 1972). Other investigators have found quantitative deficits on spatial rather than verbal neuropsychological tests (Kronfol, Hamsher, deS. Digre, & Wazir, 1978), but have failed to find deficits on simultaneous as compared to sequential methods of information processing (Gur, 1979). One study has examined the Categories Test, a measure of abstract reasoning and logical ability used as part of the Halstead-Reitan battery, to compare cognitive changes in bipolar vs. unipolar depressed patients (Savard, Rey, & Post, 1980). The study concluded that while both groups showed impairment, the deficits in bipolars were much greater and, in the case of older bipolars, often fell below performance levels expected in brain-damaged subjects. Further analysis of the Savard data subsequently revealed that the greatest differences between depressed and control groups occurred on the portion of the test which is most dependent on processing of spatial information (Silberman & Weingartner, unpublished data).

A number of studies have suggested that the cognitive impairment evident in depression occurs

in those situations or tasks that require effort, particularly sustained effort. For example, depressed patients are more likely to demonstrate impaired cognitive performance in freely remembering information rather than on tests of recognition memory. Memory-learning failures are also more likely when depressed patients are asked to accomplish tasks requiring elaborative processing and analysis of information, rather than conditions that require superficial processing of information. In a similar vein, memory failures in depression are less obvious on tests of immediate recall from short-term memory rather than delayed recall (Stromgren, 1977). Furthermore, when depressed patients are administered amphetamine, there is facilitation that is selective and restricted to tasks that require more effort (Reus, Silberman, Post, & Weingartner, 1979). In summary, it would appear that effortful processing tasks, those that require active and sustained cognitive activity, are the particular targets of disruption in depression. Recent cognitive studies have, in fact, suggested that different types of mechanisms are involved in automatic vs. effortful information processing (Hasher & Zacks, 1979). These processes are mediated by different psychobiological determinants (Lewis, 1979) and are disrupted differentially in different syndromes (Stromgren, 1977; Weingartner, Gold, et al., 1981b; Weingartner, Kaye, Smallberg, et al., 1981c). This hypothesis, namely that the cognitive information processing impairment in depression is related to an inability to sustain effort on some level, has been tested directly and confirmed. The ability of depressed patients to sustain motor effort is almost perfectly correlated with the intensity of the memory impairment evident in these patients and, together, these are highly correlated with the patient's intensity of depression (Cohen, Weingartner, Smallberg, & Murphy, in press).

While it remains for further study to clarify the psychobiological mechanisms that link effortful (or automatic processes) to cognitive failures in depression, a line of evidence with potential explanatory power is that of changes in balance between the cerebral hemispheres. There is considerable evidence to support characterization of the left hemisphere cognitive style as detailed, serial, or intentional, and that of the right as holistic, parallel, and incidental. In such terms, one might speculate that depressive deficits in effortful processing, that is, deficits in relatively deep analysis of semantic and organizational aspects of stimuli, may represent a decrement in left hemisphere cognitive functions. In support of such a speculation is a body of independent data, gathered in normal and brain-lesioned subjects, associating the left hemisphere with mediation of positive affective states, and the right hemisphere with mediation of negative affective states. Evidence for this hypothesis comes from such diverse experimental sources as lateral eye movement (Ahern & Schwartz, 1979), electroencephalographic (Davidson, Schwartz, Saron, et al., 1979), and electromyographic (Schwartz, Ahern, & Brown, 1979) studies in normals, and observation of patients with unilateral pharmacologic or anatomical brain lesions (Alema, Rosadini, & Rossi, 1961; Gainotti, 1972; Rossi & Rosadini, 1967). Thus, the hypothesis arises that depression may be a manifestation of right hemisphere activity.

In depression itself, there are also data which more directly suggest shifts in hemispheric balance or function as a concomitant of the ill state. Such diverse procedures as electroencephalography, dichotic listening, galvanic skin response, and lateral eye movements have shown results suggestive of a shift in the balance of hemispheric activity away from the left and toward the right hemisphere (d'Elia & Perris, 1973; Flor-Henry, 1979; Myslobodsky & Horesh, 1978). Such studies, as well as the neuropsychological testing described above, also suggest that the right hemisphere may not only be abnormally activated, but also pathological in its functioning during the depressed state (Buchsbaum, Carpenter, Jr., Fedio, et al. 1979; Rochford, Swartzburg, Chaudhery, & Goldstein, 1976; Roemer, Shagass, Straumanis, & Amadeo, 1978; Yozawitz, Bruder, Sutton, et al., 1979). While such lateralized changes might provide one conceptual framework for understanding cognitive deficits in depression, the evidence is as yet preliminary (Biegel & Murphy, 1971; Donnelly, Murphy, & Goodwin, 1976; Donnelly, Murphy, & Scott, 1975), without contradictions. A great deal more data need to be collected before the presence of laterality changes in depression is firmly established, or their relationship to the origin of the illness understood.

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Distinctive Features in the Cognitive Changes in Depression: Clinical and Diagnostic Implications

The cognitive impairment evident in patients in early states of a progressive dementia can appear to be superficially similar to the cognitive changes apparent in depressed patients. This similarity in the form of the cognitive impairment in depression and progressive dementia contributes to diagnostic uncertainty and consequent inappropriate treatment strategies. The fact that early-stage dementia patients are also likely to demonstrate depressive symptomatology in response to their perceived impairments compounds the difficulties involved in establishing an appropriate differential diagnosis. The laboratory findings that have established some of the mechanisms and determinants of cognitive failures in these two different types of disorders can be useful in appropriate differential diagnoses. That is, the determinants of cognitive failures in depression, as described in some of the studies reviewed above, are qualitatively different from those that account for memory-learning-attention failures in progressive dementia patients.

What are some of the distinctive features of cognitive failure in depression that might differentiate it from the cognitive changes apparent in an early stage of a progressive dementia? Depressed patients demonstrate learning and memory failures on tasks that lack easily discernible internal structure, and where the patient must impose organization for effective learning and memory to take place. For example, while recall of random words clearly differentiates the memory-learning performance of patients from undepressed controls, patients are as able as "normals" to learn and remember inherently organized information, such as semantically related words. That this characteristic of the memory-learning failure evident in depression is different from that evident in progressive dementia is illustrated by the findings in the following experiments. The details of these experiments are presented since the methods used, and the findings, can be easily translated into clinical tools for evaluating different types of cognitive impairments.

The learning-memory performance of a group of moderately depressed patients (10 males, 10 females), characterized on the basis of standard Research Diagnostic Criterian, standardized regular mood ratings, and standard psychometric testing, was compared to age-, sex-, and education-matched controls. Subjects learned and remembered different lists of 32 words including unrelated words, and organized word lists consisting of either 2 clusters of 16 words each (e.g., vegetables, parts of a house); 4 clusters of 8 words each, or 8 clusters of 4 words each. Depressed patients recalled significantly fewer words than controls [$F(1,18) = 9.4$; $p < .05$]. The interaction of type of list and groups (depressed vs. controls) was also statistically reliable using a standard repeated measures analysis of variance (ANOVA) and including all available degrees of freedom [$F(6,108) = 3.71$; $p < .01$], as well as by a conservative analysis using Winer's correction for degrees of freedom in a repeated measures design ($p < .05$). That is, depressed patients were most distinguishable from control subjects in recall of unrelated information, and this is illustrated in Figure 1.

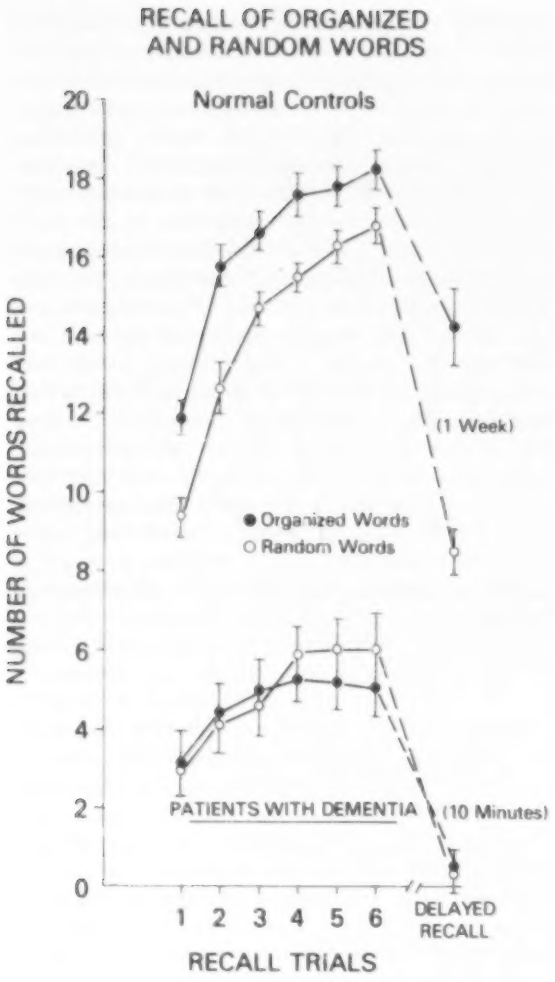

FIGURE 1. Learning and recall of random and related words by depressed patients and normal controls.

In contrast, progressive dementia patients could not use organizational or semantic relational properties of events as an aid in encoding information and, therefore, related events (words) are no more memorable than random words (Weingartner et al., 1981c). This is evident even in those patients who are no more cognitively impaired than depressed patients as measured by tests of IQ, Wechsler Memory Scale Scores, and recall of random words. Progressive dementia patients remembered about the same number of random and related events after a single exposure and after repeated presentation of information. Control subjects, as well as depressed patients, are far more successful in remembering related than random events, and this effect is enhanced with increased familiarization with that information, and also when memory is tested after a period of delay. The following experiment illustrates this aspect of the memory-learning failure in progressive dementia patients who are no more impaired than some depressed patients who have been studied using similar procedures. As will be evident, the form of the memory-learning impairment in these progressive dementia patients is quite different from that seen in depressed patients.

Fourteen patient volunteers (9 males and 5 females) were selected for further study from a much larger sample of patients after extensive systematic standardized clinical, psychometric, and neurological evaluation (for diagnostic purposes). On the basis of detailed historical, clinical, and laboratory data, a diagnosis of a progressive idiopathic dementia, probably of an Alzheimer's type, could be made. Patients, none over 65 years of age, were all in the earliest state of a progressive dementia (based on clinical data as well as psychometric findings, including IQ test scores of at least 100, and impairments in memory as measured by the Wechsler Memory Scale, normal digit span), were otherwise in good health, and were not being treated for other medical disorders. An equal number of age, education, and socioeconomic status matched control volunteers (where possible, the spouse of the patient) were also recruited and studied. Neither patients nor controls had any history of significant psychiatric disorder. Their average age was 61.2 (standard error ± 2.2), and education 14.1 years.

On separate occasions, subjects were presented with two different sets of very common words presented in a randomized sequence. One list consisted of 20 random words and the other was made up of words drawn from two superordinate categories (10 words each) of semantically related words, such as *vegetables* and *parts of the body*. After verbal presentation of each list, at a 3-second rate, immediate free recall was tested. The word list was then re—presented five times, always in a different random order, with a test of recall after each presentation. A delay period was included to measure and test the presence of information in

long-term memory. Unimpaired subjects were retested 1 week after the last learning trial while progressive dementia patients attempted another recall after a delay of only 10 minutes. This shorter delay interval was a practical necessity when testing patients with significant memory impairments.

The inability of progressive dementia patients to effectively use organizational or relational properties of to-be-remembered words was evident on immediate recall, list learning, and delayed recall following multiple list presentations of random and related words. Controls consistently remembered more related than random words and this was evident on each presentation (learning) recall trial [$F(1,13) = 18.3$; $p < .001$]. This effect was increasingly evident as list learning continued (interaction of trial × lists [$F(4,5.2) = 53$; $p < .01$]. Recall of related words was also more complete than that of random words when memory was tested one day later [$F(1,13) = 17.5$; $p < .001$]. Progressive dementia patients thus demonstrated memory-learning failures when their cognitive performance is compared to unimpaired controls. More important, and unlike the pattern of cognitive failures in depression, organization did not significantly alter any aspects of learning or memory in these patients. These findings are summarized in Figure 2.

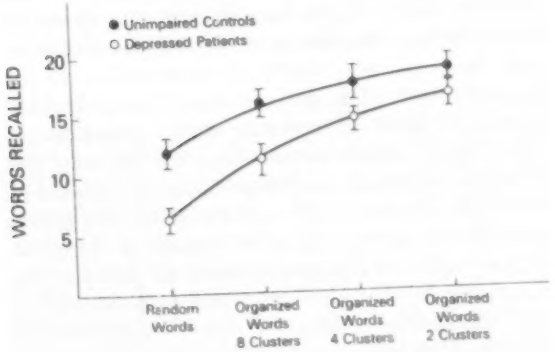

FIGURE 2. Learning and recall of random and semantically related words in patients with a progressive dementia and unimpaired controls.

As described above, laboratory studies of depressed patients demonstrate that learning and memory fail as a function of the difficulty, effort, or cognitive load required in some task. Compared to controls, depressed patients demonstrate more obvious and robust impairments when they are directed to learn and remember information (intentional learning) rather than for incidentally learned information (Weingartner et al., 1981a), when information must be "held" in memory for long rather than short time periods, for more difficult types of learning such as remembering serial order, or under more stringent and demanding remembering conditions such as free recall. As was pointed out above, the cognitive failures in depression are far less evident on "easier" cognitive tasks such as those that involve relatively "automatic," effortless, or passive operations. In contrast, progressive dementia patients fail to learn and remember despite their sustained efforts in performing cognitive operations. Unlike depressed patients, they are particularly distinguishable from controls on "passive" or "automatic" processing tasks such as estimating how often events had occurred, in contrast to freely remembering those events (a more active effortful task). The progressive dementia patient is also different from older controls, who may demonstrate changes in learning and memory requiring effortful processing but are indistinguishable from healthy young subjects on "automatic" processing tasks.

Despite the cognitive blurring and disrupted learning and memory that is apparent in depressed patients, they are able to effectively access knowledge structures such as the semantic relationships, and attributes and meanings of events, and relate this previous learning to ongoing events. For example, when either unimpaired or depressed subjects are asked to think about and say aloud words related to categories of information (such as types of flowers, parts of a house, etc.), they do so easily and are even more productive, over a 2-minute time period, than when thinking of words that might start with the same letter. On the other hand, progressive dementia patients, in generating appropriate associations to names of categories or words all starting with the same letter, are far less productive than controls or depressed patients but, more important, are particularly unproductive in generating words

that are all members of the same category (Weingartner et al., 1981c). Their productivity in generating appropriate responses from semantic memory is highly correlated with the learning-memory performance of progressive dementia patients, but this relationship is not evident in depressed patients (Weingartner et al., 1981a).

Methodological Issues

Studies that have explored cognition in depression have differed from one another in three important ways. They have varied with respect to 1) the nature of the independent variable (what constitutes depression); 2) the type of dependent measure (the target cognitive response); and 3) the assumptions and models used to generate questions about cognition in depression. Because of these differences in design, focus of study, and theoretical models used to generate studies and interpret results, it has been difficult to form a general and integrated picture of cognitive changes in depression.

Two types of independent variables have been used in cognitive studies in depression. Comparison of subject groups represents the most frequent method of manipulating depression as an independent variable. Depressed patients are often compared to some control group or to themselves in an undepressed state. One of the problems in obtaining a clear picture of the nature of cognitive changes in depression results directly from the diversity in defining what constitutes depression in some population of subjects. That is, depressed patients studied have varied with respect to the intensity of depression, forms of depressive symptoms, and sub-diagnostic categories. Studies of clinically depressed subjects have included patients who are defined as Bipolar 1, Bipolar 2, or reactive depressions, as well as other forms of unspecified clinical depressions. What can be concluded about the nature of cognitive changes in depression may be quite dependent upon not only the intensity of depressive symptoms but also the type of clinical depression that is studied. There are, in fact, data that would suggest that with respect to quantitative changes in depression, bipolar patients are more likely to demonstrate more profound changes than any other subgroup of depressed patients. Unipolar and bipolar patients, for example, have been found to differ in presenting symptomatology, Rorschach response style, and Minnesota Multiphasic Personality Inventory (MMPI) profile.

It is also not clear to what extent cognitive changes in depressed patients are state vs. trait specific. Little work has been done examining the nature of cognitive processes in patients who have recovered from some depressed episode. This type of data represents just one source of information that is necessary for appropriate evaluation and definition of cognitive changes associated with depressed states.

Other studies have defined depression as the independent variable by choosing to contrast subjects that are drawn from other than clinical populations. These have examined essentially unimpaired subjects in the psychology laboratory. In general, subjects have been selected on the basis of large sampling strategies using some standard psychometric test instrument. Depression is then defined on the basis of statistical rather than clinical criterion. A large variety of scales have been used as methods for defining such subgroups of subjects. The MMPI, the Zung, and Hamilton Depression inventories, standard clinical interviews, life-stress event scales, hopelessness scales, as well as more behaviorally and less subjectively focused scales, were designed to measure cognitive bias in depressed mood (Blaney, Behar, & Head, 1980; Hammen, in press; Krantz & Hammen, 1979; Sarason, Johnson, & Siegel, 1978; Seligman, Abramson, Semmel, & von Baeyer, 1979). These measures of behaviors that would define depression may be quite different, and the scales may also be anticipated to tap different facets of cognitive experience. Unhappiness, sadness, dysphoria, and depression are not logically equivalent. Clearly, the cognitive changes associated with depression, as defined by some psychometrically and statistical evaluation procedure, may not be at all similar to the structure of cognitive changes apparent in patients who are clinically depressed and seek help because of the disruptive effects of their experience of dysphoric mood.

The other method of defining depression, the independent variable for study, is through some behavioral manipulation of mood. Those behavioral manipulations have primarily been directed at affecting mood changes in unimpaired

normal controls under laboratory test conditions. These mood-induction procedures have been useful in inducing mild depression, which is presumed to model the kinds of dysphoric moods that are evident in depressed patients. Frequently, the manipulations used are conceptually tied to studies that would test behavior-oriented models of depression. Two types of manipulations have been used. One has involved the use of some informational context. For example, a subject may be asked to read statements that describe various moods. These are then used to provide a contextual mood-altered setting for processing information about self and others (Velton, 1968). Many subjects, when asked to read statements with dysphoric content, rate themselves as depressed, which may then be reflected in cognitive behaviors as measured by response latency and speech patterning (Natale, 1977) and other measures of cognitive efficiency. A second commonly used technique for altering mood has involved manipulations such as feedback on some task that requires skill, as in the form of a success vs. failure manipulation (Diener & Dweck, 1978; Hammen & Krantz, 1976) on a skill task. It can also involve a manipulation of reinforcing consequences or informational feedback on some task which may affect self-esteem (Coleman, 1975). Other behavioral manipulations may induce a form of helplessness through experimenter-induced failure (Abramson et al., 1968). In all of these approaches what is being tested is how a manipulation of mood, through informational or behavioral means, may affect aspects of information processing, problem solving, interpersonal perceptions, or perceptions about self. The assumption is, again, that these alterations in mood that are a product of behavioral manipulations are like those evident in depressed patients. Whether such manipulations of mood in unimpaired subjects mimic the types of cognitive changes associated with depression remains an unanswered question.

The nature of the dependent variable has also been quite different from one study to another. The kinds of cognitive measures that are used to assess performance in depressed patients, recovered patients, or normal subjects after some manipulation of mood have been quite variable. The cognitive response may be one that assesses how thoughts are organized, what is remembered, the meaning of prior-life events, how well a complex cognitive behavior is accomplished, the effectiveness in interacting with an information-rich environment, concept attainment, encoding of self, or significant others. Clearly, the kinds of changes in cognition that would occur in the depressed state would be expressed rather differently depending on the type of cognitive behaviors used as target measures for cognitive changes.

The theoretical models and assumptions that are used both to generate strategies for looking at depression and interpreting findings are also quite different from one another. These have included biological, behavioral, information processing, and psychodynamic models of depression. Unfortunately, both the nature of the findings that have been generated and their interpretation have not been easily integrated and synthesized. In part, this is due to the intrinsic differences in the language systems used to describe events in biological psychiatry, psychodynamic theory and application, and behavioral approaches to psychopathology. Investigators speak one of these languages and not others. It is, therefore, particularly difficult to relate findings generated from those very different conceptual schemes for the analysis of behavior.

There remain many unresolved questions about the psychobiology of cognitive processes in mood disorders. A good deal of work has been done, but more remains to be accomplished.

What might be some productive themes for future investigations? Clearly, cognitive changes that are apparent during periods of disordered mood must be evaluated and contrasted with cognitive processes during normal mood states in these same patients. This requires following patients systematically over time. It may also be useful to evaluate first-degree relatives of these same patients or subjects who may be considered to be at risk for affective illness. Are cognitive processes in these patients, mood-state specific or trait specific, and do the types of cognitive processes used by these subjects, while unimpaired, predict or make these subjects vulnerable to a mood disorder? Further research in this area should allow for more effective and deliberate integration of clinical material, findings from unimpaired subjects where mood is manipulated, behavioral views of mood disorder, and informa-

tion processing characterizations of cognition in mood-disorder patients. Without such integration of methods, findings, and interpretation of findings, this area of study will remain as a series of isolated efforts without the necessary research leverage that permits us to answer basic questions about cognitive processes in mood disorders.

Last, and a related issue, is the fact that although we have learned a great deal about the biology of mood disorder and about the psychology of disordered mood, surprisingly little research has been accomplished that would bring these two types of research endeavors together in a systematic manner. This may be most effectively accomplished in considering cognitive processes in the mood disorders.

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Electroconvulsive Therapy: Research Goals

Section Editors:

Richard Abrams, M.D., Professor and Vice-Chairman, Department of Psychiatry, University of Health Sciences/The Chicago Medical School, No. Chicago, IL 60064.

Jack Blaine, M.D., Research Psychiatrist, Pharmacologic and Somatic Treatments Research Branch, National Institute of Mental Health, Rockville, MD 20857.

This special section of the *Psychopharmacology Bulletin* is devoted to the proceedings of two conferences held in Chicago on November 13-15, 1980 and January 29-31, 1981.[1] The purpose of these meetings was to review the present "state-of-the-art" with regard to electroconvulsive therapy (ECT) research and to generate specific recommendations to the National Institute of Mental Health (NIMH) concerning the major research problems facing ECT investigators during the present decade. These conferences evolved from two prior NIMH-sponsored conferences on ECT. The first, "Psychobiology of Convulsive Therapy" (Fink, Kety, McGaugh, et al., 1974), attempted to define the cognitive, technical, physiological, and biochemical parameters of ECT as they were then known, drawing upon both human and animal studies. The conclusions of this conference were that there had been significant advances in ECT techniques, resulting in an overall reduction in the undesirable side effects of this treatment, and that the major unresolved issue concerned the mode of action of ECT.

The second conference, "ECT: Efficacy and Impact" (Autry, to be published), focused on the short- and long-term impact of ECT on the organism, and on an assessment of its clinical efficacy in a wide range of psychiatric disorders. This conference provided a comprehensive and detailed historical assessment of the convulsive therapy process, and concluded by addressing some of the critical research needs in the field, many of which served as foci for the 1980-1981 conferences.

After more than 40 years, ECT remains a widely used treatment in this country. An estimated 73,000 patients per year (4.4/10,000 population) receive this treatment (Fink, 1979) with greatest usage in the general hospital. About 72% of American psychiatrists believe it to be the safest, least expensive, and most effective treatment for many patients, and 22% of those sampled personally administer the treatment (APA, 1978).

This special section amply demonstrates that although much is known about ECT, more remains to be learned. It is our hope that these papers will stimulate others to investigate the problems detailed here, with the aim of developing a more rational and effective therapy.

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The Importance of Diagnostic Criteria for Depression in the Study of ECT

Michael Alan Taylor, M.D.[1]

The keystone to quality clinical research is proper patient selection based upon reliable, operationally defined diagnostic criteria. Despite the use of sophisticated laboratory procedures or potent psychotropic agents, data from studies which do not employ rigorous patient selection cannot be generalized with any assurance, and the investigators are likely to miss real effects or report spurious findings.

Prior to the 1970s, reliable psychiatric research criteria were not available. The conflicting and confusing findings of the literature of that era, in part, reflect the lack of reliable diagnostic instruments necessary to eliminate from study the false positive subject and select homogeneous samples for investigation.

Several sets of reliable and operationally defined research criteria were developed in the 1970s (Feighner, Robins, Guze, et al., 1972; Spitzer, Endicott, & Robins, 1975; Taylor & Abrams, 1978). These criteria have permitted greater precision in subject selection and have helped clarify some of the confusion generated by older studies. The exposure of the overdiagnosis of schizophrenia and the underdiagnosis of affective disorder in the pre-1970s is perhaps the most important effect of the introduction of modern criteria (Taylor & Abrams, 1978; Pope & Lipinski, 1978).

Several categories in the nosology of mental disorders remain controversial, despite the recent advances in diagnosis. This is particularly true for the category of depression. As depression is the primary indication for electroconvulsive therapy (ECT) (Taylor, in press), a clearly defined, generally accepted concept of depression is essential for research attempting to understand the ECT process. Much of the controversy revolves around the putative validity of the endogenous/nonendogenous depression dichotomy.

As initially proposed (Gillespie, 1929; Lange 1926; Kraepelin, 1921), endogenous depression referred to a syndrome reflecting some unknown morbid process characterized by a clear-cut episode of profound and unremitting sadness associated with early morning wakening, anorexia, dry-mouth, inability to cry, constipation, a diurnal cycle in which symptoms were most severe in the morning, psychomotor retardation or agitation, and feelings of hopelessness, worthlessness, and/or guilt which often resulted in delusional ideas and/or perceptional aberrations. Reactive depression referred to a less well-defined episode of dysphoria with anxiety which was responsive or reactive to environmental stimuli and was associated with weeping, initial insomnia, weight gain, and feelings of anger. The literature evaluating the efficacy of ECT and antidepressant agents (Taylor, in press; Fink, 1978; Prusoff, Weissman, Klerman, & Rounsaville, 1980; Nelson & Charney, 1981) clearly demonstrates endogenous depression to be extremely responsive to somatic treatment, whereas few reactive depressives respond to biological therapy and many are made worse. Despite the clear-cut distinction between the severe endogenous and mild reactive syndromes and their different responsivity to treatment, several investigators (Kendall, 1968; Lewis, 1934; McConaghy, Joffe, Murphy, et al., 1967; Weekowicz, Cropley, & Muir, 1971) were unable to discriminate the boundary between the two putative groups and concluded that the overlap was so great that the dichotomy was not warranted. Perhaps the best known works in this area are Kendall's (1968; Kendall & Gourlay, 1970a) elaborate discriminant function studies.

In these studies, variation of depressive symptomatology is expressed by a score on a linear discriminant function found from analyses of a number of items measured from patients originally diagnosed endogenous or nonendogenous. The distribution of the scores is then used to make inferences about the homogeneity of depression with a bimodal distribution indicative of subtypes and a unimodal distribution indicative of a single syndrome. In Kendall's two series a unimodal distribution was demonstrated. This has become the primary evidence in refutation of the endogenous/nonendogenous dichotomy. There are, however, several problems in interpreting this work. First, despite presenting a unimodal curve, many of the discriminant functions were signi-

[1]Department of Psychiatry and Behavioral Sciences, University of Health Sciences/The Chicago Medical School, North Chicago, IL 60064.

ficantly weighted in the predicted direction, and Kendall was able to correctly classify 86% of the sample. Secondly, although the overall distribution of discrimant functions did not differ significantly from a normal distribution, the chi-square reported comes close to significance, suggesting that measurement errors in the design (such as the significant difference in the sizes of the endogenous/nonendogenous groups and the lack of diagnostic criteria for patient selection) could have resulted in a Type II error, i.e., failing to find a real difference. Thirdly, demonstrating a bimodal distribution may be difficult, even for clearly different groups, if the two groups share more characteristics than the number which separates them or if characteristics are not properly weighted when some characteristics are more important than others at discriminating groups. For example, men and women have more physical characteristics in common than the number which clearly distinguishes them, and some of their distinguishing characteristics are more important than others. A discriminant function distribution curve of the sexes not adequately considering the overlap of characteristics or not weighting some characteristics might well be unimodal despite clear sexual dimorphism. Certainly, Kendall and Gourley's (1970b) inability to find a bimodal distribution for a sample of patients with schizophrenia or affective disorder suggests that this kind of analysis has limited usefulness. Finally, as Murphy (1964) and Everett (1981) have pointed out, bimodal and unimodal distributions of discriminant scores can be obtained at will from the same group of patients by choosing variables appropriately when samples are small (as in Kendall's studies), when putative subgroups are not well separated, or when the predicted variable is poorly defined (as may be the case for nonendogenous depression) (Akiskal, Bitar, Puzantran, et al., 1978; Nelson, Charney, & Quinlan, 1981) and by manipulating the class intervals for the distribution histogram. Nevertheless, some studies evaluating the power of "classical" endogenous and reactive symptoms to predict treatment response (Coryell, Ziegler, & Biggs, 1980), and one study comparing morbidity risks for affective disorder in the first-degree relatives of endogenous and reactive probands (Winokur & Pitts, 1964) also failed to support the dichotomous classification of depression.

Modern diagnostic criteria have been influenced significantly by these negative studies. The Research Diagnostic Criteria (RDC) and the Diagnostic and Statistical Manual-III (DSM-III) attempt to finesse the issue by permitting subtyping within the broad category of major depression, and by not requiring clear-cut exclusion criteria to prevent contamination between subgroups. The Feighner et al. (1972) criteria reject subtypes of depression and consider primary affective disorder homogeneous.

Nevertheless, there is significant evidence (Carroll, Feinberg, Greden, et al., 1980; Feinberg, Carroll, Steiner, & Commorato, 1979; Klerman, Endicott, Spitzer, & Hirschfeld, 1979; Nelson, Charney, & Vingaino, 1978) that the above sets of criteria select heterogeneous samples of depressives which fit more readily into the endogenous/nonendogenous classification. Feinberg's and Carroll's work (1979, 1980) typifies this literature. They and their associates challenged RDC and Feighner positive depressives, who were independently and blindly reclassified as endogenous or reactive, with dexamethasone, a highly sensitive and reliable test for discriminating depression. Forty percent of the endogenous patients failed to suppress their control levels in response to dexamethasone, whereas 98% of reactive patients showed suppression. From this and other studies, investigators estimate that of patients labeled depressed by RDC or Feighner criteria, 50 to 70% are inappropriately classified and unsuitable for research of present-day biological treatment. This estimate is supported by studies of bereavement (Bornstein, Clayton, Halikas, et al., 1973; Clayton, Halikas, & Maurice, 1972) in which nearly 50% of widowed subjects satisfied Feighner criteria for primary depression, although neither the investigators nor the "Feighner-positive" subjects felt that they were ill. There was also no evidence (e.g., past personal history of affective disorder, family history of affective disorder) that these Feighner-positive individuals were predisposed to a disease.

Further support for the endogenous/nonendogenous dichotomy derives from laboratory work studying the sedation threshold (Perez-Reyes, 1968; Perez-Reyes & Cochrane, 1967; Shagass, Neiman, & Mihalick, 1956) and growth hormone response to amphetamine (Langer, Heinze, Reim, & Matussek, 1975). The sedation

threshold is defined as the amount of barbiturate given intravenously at a fixed rate which will produce specific changes in electroencephalograph (EEG) frontal fast activity consistent with a reduction in alertness. Shagass et al. (1956) first demonstrated a significantly lower-than-normal sedation threshold in endogenously depressed patients and a significantly higher-than-normal sedation threshold in reactive depressives. This work was replicated but with considerable difficulty. More recently, Perez-Reyes, in a double-blind, well-controlled study (1967, 1968) investigated the sedation threshold using the galvanic skin response (GSR) as a validating and reliable measure of sedation threshold EEG changes and found reactive depressives, normal controls, and endogenous depressives to differ significantly in the predicted direction in their response to barbiturate on both EEG and GSR inhibition. Similarly, Langer et al. (1976) in their investigation of the hypothalamic-pituitary axis in psychiatric disorders, demonstrated that peak human growth hormone release after a single intravenous administration of amphetamine was significantly lower in endogenous depressives and significantly higher in reactive depressives as compared to normal subjects and other psychiatric patients who did not differ from the normal controls.

Recent studies of the phenomenology of depression offer further support for the endogenous/nonendogenous dichotomy (Matussek, Soldner, & Nagel, 1981). Blashfield and Morey (1979) compared the results of 11 studies which used cluster analysis to discriminate subgroups of depressives. Their analysis rejected the continuum model of depression, in which the endogenous syndrome is considered the more severe form, and the investigators concluded that as a group, cluster analytic studies demonstrate two depressive syndromes, one consistent with endogenous and one consistent with nonendogenous depression. Nelson and Charney (1981) have reviewed in great detail studies employing factor analysis, cluster analysis, discriminant function analysis, symptom frequency comparisons, and objective instrumental measures correlated with behavior (e.g., EEG recording of sleep patterns, cognitive testing) and have concluded from their review and from their own data (1981) that endogenous depression is an autonomous pathophysiological state distinct from the nonendogenous syndrome. In contrast, Akiskal et al.(1978) have demonstrated the heterogeneity and instability of reactive depression.

Thus, from treatment response, symptom pattern, and biological data endogenous depression appears to be a distinct clinical entity that is particularly reponsive to somatic treatment. As the use of DSM-III, RDC, and Feighner criteria will result in the inclusion of many false positive patients who do not have the endogenous syndrome, it is important to modify these criteria for studies of affective disorder and biological therapies.

The data summarized above suggest that this modification of present research criteria for depression is best achieved by 1) selecting patients who satisfy the inclusion criteria for melancholia or endogenous depression, and 2) excluding those who demonstrate coexisting or past behaviors consistent with anxiety states or Briquet's syndrome, who have no evidence of coarse brain disease, drug ingestion, or systemic illness known to produce depressive symptoms, and who have no concurrent alcohol or drug abuse. The Table displays these suggested criteria.

The recommendation to use rigorous criteria to identify endogenous depressives for studies of affective disorder and biological treatments does not mean that all such patients have a common pathophysiology. However, if we are to progress further in our understanding of what makes people depressed and how ECT works, the best possible delineation of depressive disorder is an essential first step.

Table

Suggested Research Diagnostic Criteria for Depression (Modified from RDC)

Inclusion Criteria (all required)

1. Must have loss of pleasure in all or almost all activities, lack of reactivity to usually pleasurable stimuli (doesn't feel much better, even temporarily, when something good happens)
2. Distinct quality of depressed mood, i.e., the depressed mood is perceived as distinctly different from the kind of feeling experienced following the death of a loved one
3. Must have two of the following present nearly every day for a period of at least 2 weeks:
   a) early morning wakening (at least 2 hours before usual time of awakening)
   b) depression is regularly worse in morning
   c) marked psychomotor retardation or agitation (but not merely subjective feelings of restlessness or being slowed down)
   d) anorexia with at least 2.5 kg weight loss
   e) excessive or inappropriate guilt (may be delusional)

Exclusion Criteria (all required)

1. No evidence of coexisting or past anxiety disorder, somatoform disorder, or disassociable disorder
2. No evidence of coarse brain disease, drug ingestion, or systemic illness known to produce depressive symptoms.

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Clinical Prediction of ECT Response in Depressed Patients

Richard Abrams, M.D.[1]

Before signing consent for electroconvulsive therapy (ECT), a therapeutic measure popularly believed to be both drastic and a last resort, patients and their families want to know the likelihood of recovery with this form of treatment and whether its potential benefits outweigh its risks. Thus the need arises for practicing clinical psychiatrists to be able to predict which depressed patients are most (and which least) likely to respond to ECT.

Hobson (1953) was the first to assess the relation of various clinical and historical features to the outcome of depressed patients treated with ECT. He recorded the presence or absence of 121 clinical features in 127 patients ("almost all" depressed), eschewing diagnostic classification as "too ill-defined and too widely inclusive" for prognostic purposes. Two weeks after a course of ECT, patients were assigned to good (62%) or poor (38%) outcome groups and each of the 121 clinical features was tested for its correlation with outcome. Thirteen features were correlated significantly with outcome: five favorable (sudden onset, good insight, obsessional previous personality, self-reproach, and duration of illness less than 1 year), and eight unfavorable (mild-moderate hypochondriasis, depersonalization, emotional lability, neurotic traits in adult life, hysterical attitude toward symptoms, intelligence above average, fluctuating course, and neurotic traits in childhood). By adding to this list three "very suggestive" features (pronounced retardation being favorable, and the ill-adjusted premorbid personality, and hysterical previous personality being unfavorable), a checklist of 16 clinical and historical features was constructed to rate each patient, assigning one point for the absence of a favorable feature or the presence of an unfavorable one. The scores ranged from 1 to 14, with lower scores indicating the more favorable outcome. When the frequency distribution of scores was compared for the good and poor outcome cases, a score of 7.5 provided the least misclassification. For example, had a good outcome been predicted for each patient with a score less than 7.5, and a poor outcome for those with a score over 7.5, outcome would have been predicted successfully in 79.7% of the cases.

Roberts (1959) correctly predicted outcome after ECT in 78% of his cases using Hobson's index, but Hamilton and White (1960) found no correlation for the Hobson score and clinical outcome in 49 depressed men receiving ECT. They applied instead the technique of multiple regression analysis to the problem, choosing five variables individually correlated with outcome: duration of illness, weight, the body index, initial depression scale score, and the fall in blood pressure with methacholine, and derived a multiple correlation with improvement of +0.62 for these combined items.

Nyström(1964) selected 24 variables correlated with outcome after ECT and calculated individual prognostic values for each patient based on the partial regression coefficients of the items. Outcome was correctly predicted in 76% of the cases. Favorable features included early morning waking, retardation, and profound depression in mood; unfavorable features included seclusiveness, ideas of reference, depersonalization, obsessionality, and histrionic behavior.

Carney, Roth, and Garside (1965) constructed a predictive index (the Newcastle Scale) for patients receiving ECT by applying multiple regres-

[1]Department of Psychiatry, University of Health Sciences/The Chicago Medical School, North Chicago, IL 60064.

sion analyses to find the weights for each of 35 clinical items which best predicted outcome 3 months after treatment. They selected five favorable features (weight loss, pyknic physique, early morning waking, somatic delusions, and paranoid delusions) and five unfavorable features (anxiety, worsening of mood in the evening, self-pity, hypochondriasis, and hysterical traits). Assigning appropriate regression weights to each item yielded for each patient a score that had a multiple correlation with outcome of ± 0.67. Each item that correlated positively with a good therapeutic outcome also correlated with the diagnosis of endogenous depression. The Newcastle Scale was subsequently tested on a new sample of 97 depressed patients by Carney and Sheffield (1972) and found to have a 76% predictive accuracy.

Mendels (1965a) found the Hobson score to predict outcome correctly 1 month after ECT in 34 of 50 depressed patients (78%). He then constructed his own index from variables selected by item analysis for their association with a significant reduction in depression scale score after ECT (1965b). Favorable items were a family history of depression, early morning waking, delusions, and psychomotor retardation. Unfavorable items included neurotic traits in childhood or adulthood, inadequate premorbid personality, precipitating factors, and emotional lability. Mendels correctly predicted the response to ECT at 1 month in 90% of his cases and, in a subsequent study with an additional 50 cases, a slight modification of the index yielded a predictive accuracy of 86% (1967).

A few individual variables have been reported to predict a favorable response to ECT, including cyclothymic personality (Abrams & Taylor, 1974; Ottosson, 1962) and pyknic physique (Abrams & Taylor, 1974). Perris (1966) observed that bipolar patients had a better response to ECT than unipolar patients, but our own study failed to confirm this (Abrams & Taylor, 1974).

The prognostic accuracy reported for the various indices may be statistically inflated. Selecting items significantly correlated with outcome from a larger group of items tested and combining them in a coefficient of multiple correlation overestimates the relationships involved. The problem is compounded when the indices are then used to predict outcome in the sample from which they were derived. It is also necessary to consider the accuracy of the predictive indices in comparison with simply giving ECT to all depressed patients referred for treatment or only to those with the diagnosis of endogenous depression. In Hobson's study (1953), a 61.8% predictive accuracy would have been achieved simply by giving ECT to every patient. In Mendels' study (1965b), this procedure would have been correct 60% of the time. If ECT were given only to patients with well-defined symptoms of endogenous depression, the predictive accuracy would have been 72% in Mendels' study (1965b) and 73% in Carney and Sheffield's study (1972).

Abrams, Fink, and Feldstein (1973) tested the predictive value of the indices of Hobson (1953), Carney et al. (1965), and Mendels (1965b) in a sample of 76 hospitalized primary depressives referred for ECT. They found no relation between any of the three indices and improvement as measured by the residual post-ECT Hamilton Depression Scale score, adjusted to account for the variance of the pre-ECT score. In addition to the individual items needed to calculate the three indices, they assessed the presence or absence of a number of other features possibly related to outcome with ECT, including a history of mania or hypomania, cyclothymic personality, endogenous mood swings, a history of prior depression, and impaired concentration. There were 22 variables in all, none of which demonstrated a significant correlation with outcome.

In retrospect, it is felt that negative results obtained by Abrams et al. (1973) were probably due to selection bias. He studied an older group of hospitalized patients (mean age = 63.7 years) who were much more likely to fit the category of endogenous rather than reactive depression, thus virtually eliminating the powerful negative predictive variables associated with reactive depression. To test this hypothesis, an analysis was done of the data on all depressed patients who participated in a series of ECT studies conducted by Taylor and the author over a period of 10 years (Abrams & Taylor, 1973, 1974, 1976; Abrams, Taylor, Faber, et al., in press). Each patient satisfied research criteria for endogenous depression and each was blindly rated before and after a course of ECT using a modified Hamilton Rating Scale for Depression. Hierarchical multiple regression analysis was used to examine the relation between each of the depression scale items

and the post-ECT depression score, which was adjusted to account for the variances of the pretreatment depression score, treatment electrode placement, sex, and the total number of treatments received. In a sample of 97 endogenous depressives, a significant correlation was found only between one individual item (gastrointestinal symptoms) and the adjusted post-ECT depression score, well within the boundaries of chance. It would appear, then, that once a population of endogenous depressives is specified, there is simply not enough variability left from which to predict outcome.

In summary, the various clinical predictive indices have only limited application today. The individual clinical features comprising each index are, after all, only manifestations (epiphenomena) of an underlying disorder of presumed biological origin, variously termed endogenous depression or melancholia. Patients with this disorder have been universally demonstrated to respond to ECT, and the predictive indices probably do little more than attempt to identify such patients more systematically than is usual. What is needed is a biological measure of melancholia which is independent of the vagaries of clinical presentation. The dexamethasone suppression test is an important first step in the development of such a measure and will doubtless be further refined, or followed by other more accurate procedures, to ultimately yield a specific test for the prediction of response to ECT. The thrust of future research into the prediction of ECT response should be along these lines.

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Predictors Of Outcome In Convulsive Therapy

Max Fink, M.D.[1]

With the introduction of treatments with inherent risk for the mentally ill, such as arsenicals and fever therapy for neurosyphilis, and insulin coma, convulsive therapy, and leucotomy for schizophrenia, predictors with specificity for a favorable outcome became matters of high priority. In studies of schizophrenia, both insulin coma and leucotomy were found to have limited ap-

[1]Department of Psychiatry and Behavioral Science, School of Medicine, State University of New York at Stony Brook, Long Island, NY 11794.

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plications. But convulsive therapy was effective in melancholia, mania, and catatonia. A search was focused on finding an analog of the Wasserman test for syphilis—a simple procedure with high specificity for a common pathogenesis. Such identification is essential to the development of a safe and rational therapy. It is the aim of this review to cite the principal studies in the search for predictors of outcome in convulsive therapy. While no recent measure fulfills the criteria of specificity, safety, and ease of administration of the Wasserman test, the variety of measures under study, when integrated with the present knowledge of the physiologic effects of induced seizures, and the objective methods of classification of the mentally ill, provide a basis for enthusiasm in the ongoing search.

The empirical nature of convulsive therapy has led investigators to seek specific predictors of outcome in three broad dimensions—clinical criteria, personality and psychologic tests, and biochemical and physiologic laboratory tests (Fink, 1968, 1979). Much of the data of studies done between 1938 and the early 1960s, prior to the introduction of modern psychotropic drugs, are no longer applicable. The argument in the early days was the selection of patients for convulsive therapy, leucotomy, and insulin coma, with hospitalization, moral, and milieu therapies as the principal alternatives. Not only did the treatments differ, but the population samples referred to research centers differed. The present samples reflect the residue of those severe mentally ill patients already treated with active psychotropic substances. Nevertheless, a review of the early concepts provides a basis for our present studies.

Clinical Criteria

The most widely used and best criterion for the selection of patients for convulsive therapy is clinical diagnosis—the type and severity of the pathology, and the recent medical history. Despite changes in clinical typologies, represented by the general acceptance of the Research Diagnostic Criteria and the Diagnostic and Statistical Manual-III (DSM-III) schemata, patients who are severely ill, with syndromes of melancholia (endogenous depression, primary depression), catatonia, and mania have the best prognosis for short-term outcome with electroconvulsive therapy (ECT) (APA, 1978; Fink, 1978, 1979; Scovern & Kilmann, 1980; Ottosson, 1981; Kendall, 1981). ECT is also the preferred treatment for those patients with recurrent depressions who have not responded to drug treatments in the past, and who have responded to ECT.

Within the broad syndrome of melancholia, two specific subtypes are especially responsive to convulsive therapy—patients with catatonic features (Roth & Rosie, 1953; Breakey & Kala, 1977; Regestein, Alpert, & Reich, 1977; Fink, 1979), and those with delusions of guilt or somatic delusions (Hordern, Holt, Burt, & Gordon, 1963; Glassman, Kantor, & Shostak, 1975; Avery & Winokur, 1977; Davidson, McLeod, Kurland, & White, 1977; Kantor & Glassman, 1977; Nelson & Bowers, 1978; Minter & Mandell, 1979a,b; Kaskey, Nasr, & Meltzer, 1980; Charney & Nelson, 1981). These patients respond poorly to tricyclic antidepressant medications (Rao & Coppen, 1979; Brockington, Kendell, Kellett, et al., 1978). There is also a subgroup of patients with confusional syndromes, such as the unusual cases of acute delirium, periodic confusional states, and delirious states complicating organic illnesses who respond dramatically to ECT, often to only a few treatments (Ottosson, 1981).

Many authors proposed prognostic indices, based primarily on symptoms and observable clinical signs (Hobson, 1953; Carney, Roth, & Garside, 1965; Mendels, 1965, 1967; Nyström, 1965; Pilowsky & Boulton, 1970; Weckowicz, Yonge, Cropley, & Muir, 1971). While these indices are useful in identifying the responsive subtypes in the initial samples, their application to new populations found them no more useful than clinical diagnosis alone, and they have not been generally adopted (Abrams, Fink, & Feldstein, 1973; Kiloh, 1977; Ottosson, 1981; Kendell, 1981). A good response is associated with the "endogenous features" of terminal insomnia, morning aggravation, self-denigration, weight loss and anorexia, retardation, and agitation. It is possible that the vegetative symptoms which are given the most weight in these indices reflect features in the pathogenesis of a syndrome of melancholia, which is particularly responsive to induced seizures. As these symptoms are associated with dysfunction of brainstem mechanisms, particularly hypothalamic-pituitary functioning, it is not unexpected that

some recent concepts of the mode of action of ECT focus on dysfunctions of these structures (Fink, 1979; Fink & Ottosson, 1980).

Psychologic Tests and Personality Measures

Most clinicians note that an "adequate personality" is a good prognostic feature (Kiloh, 1977; APA, 1978; Ottosson, 1981). In some early studies of convulsive therapy, the relation of psychological tests to outcome was sought. Interest was shown in the syndrome of anosognosia and denial of illness—a syndrome which is seen in patients with generalized dysfunction of the brain. It is exaggerated by the administration of sedative drugs, like amobarbital (Weinstein & Kahn, 1955). In patients undergoing ECT, the development of an organic mental syndrome is easily documented, with the severity of the syndrome proportional to the number and frequency of seizures. In such patients, a denial personality (Kahn & Fink, 1959), high acquiescence score on social attitude scales (Kahn, Pollack, & Fink, 1959, 1960a), errors on figure-ground tests (Kahn, Pollack, & Fink, 1960b), and restricted performance on the Rorschach test (Kahn & Fink, 1960) were associated with a good clinical outcome (Fink, 1968, 1979). These studies also found that older patients of foreign birth had better prognoses with ECT than younger patients who were native born in the U.S. (Kahn et al., 1959). These tests never achieved general acceptance, in part because interest in ECT waned as antidepressant drugs were introduced, and, in part, because there was little evidence that these tests were useful in distinguishing the patients responsive to ECT from those who responded to other antidepressant treatments.

Physiologic and Biochemical Tests

In the almost 50 years since the introduction of convulsive therapy, many physiologic and biochemical measures have been examined in relation to a course of ECT. Most studies assessed the effects of repeated seizures on body physiology, but a few examined the possibility that dysfunctions in physiologic and biochemical measures were related to prognosis (Fink 1968, 1979).

Tests of autonomic reactivity were a feature of early studies. A common index was the change in blood pressure in response to subcutaneous or intramuscular methacholine or to intravenous epineprine. The rate of change, the peak change, and the rate at which the blood pressure returned to baseline were examined, with a systolic rise greater than 50mm Hg after epinephrine and a delayed return to baseline greater than 25 minutes after methacholine as good prognostic signs for ECT (Funkenstein, Greenblatt, & Solomon 1948, 1950, 1952). These observations were corroborated, but later reports noted that the correlations could largely be explained by age and the basal blood pressure (Blumberg, Cohen, & Miller, 1956; Roberts, 1959a,b; Hamilton & White, 1960; Rose, 1962; Thorpe, 1962). Correlations were best in older patients with defined hypertension.

Electrophysiologic Tests

Others studied the resting EEG before treatment and found better clinical results in those patients with normal (alpha) EEG records than in those with low voltage fast records (Turner, Lowinger, & Huddleson, 1945; Weil & Brinegar, 1947; Kennard & Willner, 1948; Mosovich & Katzenelbogen, 1948); but others failed to find such an association (Moriarty & Siemens, 1947; Chusid & Pacella, 1952). Indeed, Hoagland, Malamud, Kaufman, & Pincus (1946) found a positive relationship between the amount of EEG fast activity in the pretreatment electroencephalogram (EEG) and clinical outcome with ECT in a group of involutional depressed women.

The inflection point in the increase in EEG beta activity after the intravenous administration of amobarbital (0.5 mg/kg/40 sec) was defined as the "sedation threshold," with low thresholds being positively correlated with diagnoses of psychotic depression and good prognosis with ECT (Shagass 1954, 1957; Shagass & Naiman, 1956). These findings were confirmed by some observers (Nymgaard, 1959; Perris & Brattemo, 1963), but not by others (Ackner & Pampiglione, 1959; Roberts, 1959b).

Roth (1951) reported a better prognosis with ECT for patients in whom the resting EEG delta

activity was enhanced by intravenous thiopental given a few hours after the first to third seizures. In a replication and followup study, Roth et al. (1957) reported that enhanced EEG slowing after pentothal was not related to the short-term evaluations of outcome, but to the likelihood of relapse after 3 and 6 months, with higher relapse rates in patients with lower EEG slow wave values. In parallel studies, Fink and Kahn (1957) found that the early and sustained development of high voltage EEG slow wave activity in the resting interseizure record was a good prognostic sign for short-term outcome evaluations with ECT. But this study also was not confirmed in a later series (Volavka et al., 1972; Volavka, 1974). We concluded that the earlier findings (like those with the sedation threshold and blood pressure studies) resulted from the mixed population samples (schizophrenic and depressed) studied at the time, and that such measures were not particularly useful in the more homogeneous depressed samples under study at present (Fink, 1979). The data still leave the possibility that such physiologic measures, when applied to mixed samples, identify subpopulations (such as depressed and catatonic patients) with characteristics that are particularly responsive in their behavior and physiology to induced seizures, in contrast to others (such as schizophrenic patients) who lack such responsivity.

Interest was also shown in the changes in averaged sensory-evoked responses, both as indices to identify subpopulations of the mentally ill and as indices to relate to outcome. Much of this work has been done by Shagass (1972, 1980), but its complexity and limited specificity has not encouraged its widespread use.

The sleep EEG, with measurement of rapid-eye-movement (REM) features, has been another source of indices of depressive illness and outcome with treatment. A prominent feature of depressive patients is a shortened time from sleep onset to the first REM period and a greater amount of REM activity. The changes in sleep characteristics are reversed by ECT (Kupfer et al., 1980, 1981).

One author has suggested that total seizure time may be an analog of the plasma level of antidepressant drugs, to provide a "therapeutic window" for a course of ECT (Maletzky, 1978). He noted that total seizure durations less than 210 seconds are much less effective than courses where the total seizure time was between 210 and 750 seconds.

Biochemical Measures

The biochemical effects of repeated seizures have been studied extensively and the reviews find consistent changes in brain tissues, CSF, blood, and urine (Essman, 1973; Fink, Kety, McGaugh, & Williams, 1974; APA, 1978; Fink, 1979). But the changes have not been related to clinical course, and none is useful as a predictor of clinical outcome. In studies of antidepressant medication, levels of urinary MHPG have been suggested as useful indices in the selection of different tricyclic antidepressants, but a study of its prognostic value in ECT did not confirm a relationship (Steiner et al., 1979). Studies of urinary cyclic AMP showed an increase with treatment (Hamadah et al., 1972; Moyes, 1972), while Choi, Taylor, and Abrams (1977) reported levels of calcium ATPase levels to be low in depression and to increase with treatment. In none of these studies is the relation to outcome defined.

An interesting relationship to outcome may be inferred from studies of calcium metabolism. A number of studies report decreased urinary, plasma, and CSF levels of calcium during a course of ECT, at a time when clinical improvement is noted, suggesting that the transfer of calcium into brain tissues is a feature of the therapeutic process (Flach, 1964; Faragalla & Flach, 1970; Carman & Wyatt, 1977). These observations suggest that monitoring plasma or urinary calcium may be a useful measure to relate to clinical outcome.

Neuroendocrine Measures

Recent studies of neuroendocrine relations in depressive illnesses provide the most interesting of the laboratory predictors. In some forms of depression, predominantly in endogenous depression or melancholia, neuroendocrine abnormalities are present in the absence of defined endocrinologic disease. The most extensively studied functions are those of the hypothalamic-pituitary-adrenal (HPA) axis (Carroll et al., 1976a,b), and the hypothalamic-pituitary-thyroid (HPT) axis (Loosen & Prange, 1980). An overactivity of the HPA axis is reflected in elevated plasma cortisol, loss of its diurnal rhythmicity,

and its resistance to suppression (or early escape from suppression) by oral dexamethasone. This last abnormality has been reported in up to 50% of patients with melancholia, and is now seen as having diagnostic significance (Carroll et al., 1981). Hypoactivity of the HPT axis, as reflected in a blunted release of thyroid stimulating hormone (TSH) in response to intravenous thyrotropin releasing hormone (TRH), is also found in about 25% of patients with melancholia (Kirkegaard, 1981).

Normalization of the dexamethasone suppression test (DST) with clinical recovery is well documented (Greden & Carroll, 1979; Brown, Johnston, & Mayfield, 1979; Gold et al., 1980b; Greden et al., 1980; Papakostas et al., 1981). The DST and TSH tests in 50 hospitalized male veteran psychiatric patients with various psychiatric diagnoses were examined (Papakostas et al., 1981). Of 20 cases of unipolar melancholia, 17 exhibited hypercortisolism, and 14 failed to suppress plasma cortisol after dexamethasone. The measures were repeated in 14 unipolar depressed patients after a course of ECT. Improvement in psychopathology was directly related to normalization of the HPA functions. In the followup period at 9 months, the patients with normal HPA functions had better long-term prognoses than those with abnormal functions at the end of a course of ECT. It was concluded that normalization of HPA dysfunction could be used as an index of the end of a course of ECT, suggesting that clinicians should consider further treatment in those patients who continue to exhibit hypercortisolism or an abnormal DST after a series of ECT. Similar findings have been reported by others (Dysken et al., 1979; Albala & Greden, 1980; Greden et al., 1980; Albala et al., 1981). Similar neuroendocrine abnormalities and their response to ECT have been reported in patients with catatonia, suggesting that the tests are related to abnormalities in pathophysiology responsive to ECT, and not to a specific type of psychopathology (Brown, Johnston, & Mayfield, 1979; Dysken et al., 1979; Greden & Carroll, 1979).

Findings with the TRH test did not relate to psychopathology, nor did they change with ECT. The data are inconclusive, as the samples are small. Others found the TRH test to show similar changes with treatment for endogenous depression, and further study is needed (Mendlewicz et al., 1979; Kirkegaard & Bjørum, 1980; Asnis et al., 1980; Gold et al., 1980a; Loosen, & Prange, 1980; Kirkegaard, 1981).

Other indices of abnormal neuroendocrine response in patients with depression have been described (Fink, 1980). The release of growth hormone by hypoglycemia, L-dopa, and TSH is either reduced or lacking, and returns to normal with treatment. The prolactin response to carbidopa (Garfinkel et al., 1979), the corticosteroid response to methylamphetamine (Checkley, 1978, 1980), and the growth hormone response to amphetamine (Matussek, 1978) and to clonidine (Laakmann & Benkert, 1978; Matussek et al., 1980) characterize patients with severe depression. These studies, like those of the pituitary-thyroid axis, require additional work before their usefulness as prognostic indices can be fully assessed.

Conclusion

Many measures have been examined in the continuing search for a simple, specific, and safe laboratory test which may be used to identify patients for whom convulsive therapy may be helpful. There has also been some interest in using changes in some measures as endpoints to a therapeutic series. The degree of EEG slowing in the interseizure EEG, either at rest or after a challenge dose of a sedative drug; the onset of the first REM period in sleep; plasma and urine calcium levels; and neuroendocrine measures, particularly measures of plasma cortisol and some variation of steroid suppression tests, are of special interest in continuing studies. The TSH response to TRH, as a representative of other neuroendocrine systems, and the total seizure time are also of interest. The most compelling observation is the possibility that the DST, in those patients in whom it is abnormal before ECT, may be an index to the termination of a course of successful therapy.

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Relevance of Neuroendocrine Strategies Electroconvulsive Therapy Research

Roger F. Haskett, M.B.B.S.[1], and A. Arlav Albala, M.D.[1]

Introduction

Neuroendocrine strategies are a relatively recent addition to clinical psychiatry. The techniques developed from the observation that endocrine function was often altered in association with abnormal mental states. The theoretical rationale for the use of peripheral hormone measurements as biological markers of psychiatric illness was provided by the identification of functional links between the hypothalamus and anterior pituitary gland. These connections provided the mechanism whereby the limbic system dysfunction associated with psychiatric illness could directly interfere with neuroendocrine regulation. Like the clinical endocrinologists who developed these strategies, psychiatrists have found that measurement of basal hormone levels alone will not generally provide very specific information. Abnormalities of neuroendocrine regulation appear to be more precisely identified by dynamic studies of endocrine function such as stimulation or suppression tests.

A number of studies have demonstrated consistent abnormalities of the hypothalamic-pituitary-adrenal (HPA) and hypothalamic-

[1]Department of Psychiatry, University of Michigan, Ann Arbor, MI 48109.

pituitary-thyroid (HPT) axes in patients with melancholia. Evidence is accumulating that two neuroendocrine strategies, the Dexamethasone Suppression Test (DST) and the Thyrotropin-Releasing Hormone Stimulation Test (TRH Test), which examine the function of the HPA and HPT axes, respectively, have clinical utility in the study and management of melancholia.

The Desamethasone Suppression Test (DST)

This strategy evolved from a procedure described by Liddle (1960) for the evaluation of HPA axis dysfunction in Cushing's disease. When normal subjects receive a dose of 1 or 2 mg dexamethasone at midnight, plasma cortisol levels are suppressed for at least the next 24 hours. During the 1960s, several investigators reported that, in addition to secreting excessive amounts of corticosteroids, the HPA axis in some patients with melancholia is abnormally resistant to suppression by dexamethasone. Subsequent studies have confirmed this finding and developed the DST procedure to give optimal test results for the diagnosis of melancholia (Carroll, et al. 1981). Cortisol levels are measured at 4 p.m. and 11 p.m. after administration of 1 mg dexamethasone at 11:30 p.m. on the previous day. This form of the DST identified the syndrome of melancholia with a sensitivity of 67% and specificity of 96% when administered to psychiatric inpatients.

The Thyrotropin-Releasing Hormone Stimulation Test (TRH Test)

The TRH Test used in psychiatric studies is identical to the one devised by endocrinologists for the study of HPT disorders. The test is usually conducted at mid-morning, when spontaneous plasma TSH level fluctuations are least, after an overnight fast. After drawing one or two baseline blood samples, TRH is administered intravenously over a 30-second period. Subsequent samples are obtained 15, 30, 60, and 90 minutes after TRH administration. Most of the studies have used TRH doses of either 200 or 500 μg. TSH concentrations are determined by radioimmunoassay (RIA), and the maximal change in TSH (Δ TSH) is obtained by subtracting the baseline TSH value from the maximum TSH level after TRH administration.

Since the first reports showed that a proportion of depressed patients have blunted TSH responses to TRH (Kastin, Ehrensing, Schalch, & Anderson, 1972; Prange, Wilson, Lara, Alltop, & Breese, 1972), many investigators have replicated and extended those findings. Review of these studies reveals that between 25 and 30% of euthyroid depressed patients have blunted responses to TRH, regardless of whether a dose of 200 μg or 500 μg of TRH is used in the test. With so insensitive a test, the diagnostic utility of the test is probably low. Despite this limitation, there is some evidence that treatment-associated changes in the TRH Test may serve as predictors of outcome of the acute episode.

Questions For ECT Research

Since the syndrome of melancholia is the most widely accepted clinical indication for ECT, the information obtained from melancholic patients using these two strategies and their relevance to ECT research should be examined. Although similar techniques are likely to be helpful in defining the therapeutic mechanism of ECT, there have been few human studies on this subject. This discussion will be confined to the relevance of the DST and the TRH Test to the study of ECT in clinical practice.

The information provided by these neuroendocrine strategies may be used to examine three important questions. How can ECT-responsive patients be identified and, in particular, for which patients is ECT the *most* effective form of treatment? Can the therapeutic action of ECT be monitored by changes in biological markers and will these markers indicate the optimal endpoint for a course of ECT? Is it possible to predict which patients require continuation therapy to prevent relapse after a successful course of ECT?

Selection Of ECT-Responsive Patients

In addition to being a diagnostic aid in patients

with melancholia, there are several reports which indicate that the presence of an abnormal DST may be useful as a predictor of response to treatment. Some studies suggest that patients with melancholia and an abnormal DST result have a better response to antidepressant treatment than similar patients with a normal DST result (Brown & Shuey, 1980; Greden et al. 1981). Another study reported that the DST result was more effective than clinician's judgment in predicting response of depressed catatonics to thymoleptics (Carman, Hall, Wyatt, & Crews, 1980).

It remains unclear whether the DST can identify particular melancholic patients who will respond better to ECT than antidepressant medication. There are two subgroups of patients with melancholia who generally have an excellent response to ECT and are more likely to be unresponsive to antidepressant medications. These are depressed patients with a catatonic syndrome and patients with an affective psyhcosis. Melancholic patients with psychosis may have a higher frequency of abnormal DST results than is generally present in melancholia (Carroll et al. 1980; Rudorfer, Hwu, & Clayton, 1982). In addition, retrospective examination of DST results in patients referred for ECT by clinical criteria alone shows a very high frequency of abnormal DST results (Papakostas, Fink, Lee, Irwin, & Johnson, 1981; Albala, unpublished data). These observations cannot demonstrate a relationship between an abnormal DST result in melancholia and good response to ECT. This possible association requires examination in a prospective study which controls for the psychotic and catatonic subtypes of melancholia, and compares the pretreatment DST result with the relative efficacy of antidepressant medication and ECT.

There have been no prospective studies to suggest that the TRH Test can be used to predict response to ECT. If the data reported by Papakostas, et al., (1981) are re-examined using the Δ TSH criterion of less than 7 μU/ml as suggested by Gold, Pottash, Extein, Martin, Howard, Mueller, and Sweeney (1981), it is evident that six out of seven patients with an abnormal TRH Test responded to ECT, whereas only one out of four patients with a normal TRH Test showed a good response. These data suggest that the relationship of the TRH test to prediction of ECT response deserves further examination.

Determination of Endpoint for a Course of ECT

One of the important problems faced by the clinician using ECT is to determine when a course is complete. In an attempt to lessen memory impairment, it is advisable to give the least number of ECT treatments necessary to induce relief of symptoms and prevent an early relapse. However, as discussed separately (*see* Haskett, pp. 75-78) no reliable criterion exists for determining the optimal number of ECT necessary to treat a specific patient. There are indications that the DST can provide some information on this subject.

Several investigators reported the results of serial DSTs performed throughout a course of ECT. Dysken, Pandey, Chang, Hicks, and Davis (1979) reported a case of a 56-year-old man with a diagnosis of major depressive disorder, psychotic and endogenous subtype, who was treated with ECT and had weekly DSTs throughout his treatment. They found that the abnormal DST results observed prior to treatment steadily normalized in association with clinical recovery. In another case report, Albala, Greden, and Carroll (1980) performed weekly DST assessments on a 69-year-old woman who was being treated with ECT. The abnormal pretreatment DST results normalized after the third ECT even though her depressive symptoms remained quite prominent. Further treatment resulted in good clinical recovery. More recently, Rothschild and Schatzberg (1982) reported the case of a 39-year-old man with a psychotic depression in whom the DST was performed serially during two courses of ECT. Each time, the DST normalized prior to complete, yet short-lived, clinical recovery.

Albala, Greden, Tarika, and Carroll (1981) selected a group of six unipolar endogenous depressives with abnormal DST results prior to treatment and who were treated with ECT. The DST was repeated every 5 to 7 days throughout treatment. Five out of the six patients responded favorably to ECT. The DST result in all responders normalized early in treatment despite only modest clinical improvement. Further ECT resulted in complete clinical recovery and a per-

sistence of normal DST results. The single patient in whom DST normalization was not observed failed to respond to treatment. Similar results were reported by Schlesser and Rush (1981) who studied 12 endogenous depressives with abnormal DST results. They found that at mid-treatment six of the eventual 10 responders had normal DST results, and by the end of treatment the DST was normal in all 10 responders. In contrast, the two patients who did not respond to ECT continued to show abnormal DST results.

These findings seem to indicate that during the ECT-induced clinical improvement, the post-dexamethasone cortisol levels decrease and eventually normalize. This pattern is only observed among ECT responders and does not occur in patients who have a poor outcome to the treatment. This suggests that the DST can be used as a biological monitor of clinical response to ECT. Another aspect of these studies is the timing of the DST normalization in relation to clinical improvement. DST normalization precedes complete clinical recovery and accurately identifies the eventual ECT responders. This finding has important implications for the clinician who may be inclined to stop a course of ECT because of no apparent response. The presence of a normalized DST may indicate that extra treatments will eventually result in good clinical recovery.

Theoretically, serial TRH Tests may also yield information which is potentially useful in the clinical management of patients receiving ECT. This would particularly apply to those depressed patients who have a normal DST result and an abnormal TRH Test result. The existence of such a patient population has been demonstrated by Extein, Pottash, and Gold (1981) who conducted both DSTs and TRH Tests on patients diagnosed as major depressive disorder, primary subtype. They found that 34% of these patients had an abnormal TSH response to TRH in the presence of a normal DST result. Serial TRH Tests have been done in a group of 21 unipolar patients treated with clomipramine (Langer, Schönbeck, Koinig, Lesch, Schüssler, & Waldhäusl, 1980). The data suggested a significant statistical correlation between clinical improvement and increased TSH response to TRH. A similarly designed study with ECT-treated patients has not been reported and is necessary to evaluate the potential use of the TRH Test as a monitor of clinical response to ECT.

Prediction of Relapse After ECT

The incidence of relapse after successful treatment of ECT is reported to be very high. This is discussed in more detail elsewhere (*see* Haskett, page). It would be extremely valuable if tests could identify those patients who are more likely to experience an early relapse. This would permit a clinician to prescribe continuation therapy for those patients who require prophylaxis after completion of a course of ECT. Several studies suggested that lack of DST normalization may predict early relapse despite apparent clinical remission of the depression (Greden, Albala, Haskett, James, Goodman, Steiner, & Carroll, 1980; Goldberg, 1980; Gold, Pottash, Extein, & Sweeney, 1980; Papakostas et al., 1981).

In two of these studies specific data regarding ECT-treated patients are available. Greden et al. (1980) reported 14 patients with abnormal pretreatment DST results. Four of these patients were treated with ECT and all responded to treatment. Three responders had a normal DST after ECT and remained asymptomatic for at least 7 months. One patient clinically improved after the course of ECT, but did not show normalization of the neuroendocrine disturbance. She was admitted 6 weeks later for treatment of a relapse with a second ECT course which resulted in both clinical recovery and DST normalization. She subsequently remained asymptomatic for at least 1 year. Papakostas et al. (1981) presented a series of 14 unipolar depressed patients who were treated with ECT. Nine patients eventually responded to treatment and eight of these had pretreatment post-dexamethasone cortisol levels in excess of 5 μg/dl. At discharge, the DST result had normalized and all had a good outcome for 1 to 9 months. The three patients who responded clinically but still displayed abnormal DSTs had a poor outcome. Two were readmitted within 2 months and the third committed suicide 4 weeks after discharge.

These data suggest that persistently abnormal DST results after a course of ECT predict a poor outcome and a high risk for relapse, even where clinical recovery appears adequate. Conversely,

clinical recovery accompanied by DST normalization may be a predictor of good outcome. An exception to this appears in a case report by Rothschild and Schatzberg (1982). Their patient was successfully treated with ECT, and normalization of the DST occurred. The patient, however, quickly relapsed and the DST again became abnormal. A second ECT course produced good clinical response and DST normalization. Still a second relapse occurred in association with an abnormal DST. Remission and DST normalization were eventually accomplished and maintained with the use of amoxapine. In this case DST normalization failed to predict a good outcome and was associated with rapid relapse. An alternative explanation is that this patient may have been a "rapid cycler" (Dunner, Patrick, & Fieve, 1977), and every relapse could have represented a new episode rather than a reemergence of the original episode. Greden, DeVigne, Albala, Tarika, Buttenheim, Eiser, and Carroll (1980) have shown that DST results can rapidly change in association with mood shifts in rapid cycling bipolar patients.

Several studies have reported on repeat TRH Tests after clinical recovery (Kirkegaard, 1981). It is apparent that some patients do not show a normalized TRH Test result despite clinical recovery. This suggests that, as mentioned in the previous section on the DST, antidepressant treatment can have a symptomatic effect in some patients without altering the neuroendocrine disturbance. Kirkegaard (1981) has reported that the persistence of abnormal TRH Test responses after clinical recovery predicts early relapse. In their study of 66 "clinically cured" patients, antidepressant therapy was withdrawn after clinical recovery and the patients were followed for at least 6 months or until relapse. They showed that ΔΔ TSH values (Δ TSH at discharge - Δ TSH on admission) clearly distinguished good prognosis from poor prognosis patients. The ΔΔ TSH criterion value of 2.0 μU/ml predicted cure in 27 out of 29 patients and relapse in 33 out of 37 patients. Most of the patients with little treatment-associated improvement in their neuroendocrine disturbance (ΔΔTSH < 2μU/ml) relapsed within 4 months. In contrast, the patients with ΔΔ TSHs > 2.0 μU/ml had a good outcome during the first 6 months after discontinuation of antidepressant treatment. This group of patients includes a subset of 35 patients with endogenous depression who were treated with ECT. All 19 patients with ΔΔ TSH ≤ 2.0 μU/ml relapsed within 6 months of completing the ECT course. By comparison, only 3 out of 16 patients with ΔΔ TSH > 2.0 μU/ml suffered a relapse. The relapse rates were similar among unipolars and bipolars (Kirkegaard & Bjorum, 1980). These results strongly suggest that normalization of the TRH Test, as defined by Kirkegaard, can be a reliable indicator of cure and therefore identify those patients who require maintenance antidepressant therapy to prevent relapse. A replication of this study is required.

In the series of patients presented by Papakostas et al. (1981), three of the nine ECT responders had blunted TRH Test results (≤ 5.0 μU/ml) prior to treatment. In two of these cases the TRH Test was repeated and remained blunted (one with a ΔΔTSH < 2.0 μU/ml and the other with a ΔΔ TSH > 2.0 μU/ml). Neither relapsed during a 9-month followup period. The third patient with a blunted response on admission committed suicide 1 month after discharge. No repeat TRH Test was available in this case. The number of patients in this study is too small to draw any conclusions on the prognostic value of the TRH Test.

Conclusion

This review of neuroendocrine studies has been unable to provide definitive answers to the previously stated questions for ECT research. There is, however, much evidence that this area of investigation is likely to be helpful in the future. It is unlikely that a single neuroendocrine test will be able to select those patients requiring ECT in preference to other antidepressant treatment. Combination of neuroendocrine testing with other laboratory markers, or clinical subgrouping of syndromes, may however be successful in providing objective indications for ECT. The relationship of the normalization of neuroendocrine function to the therapeutic mechanism of ECT requires further examination. It may be possible to use these markers to more precisely determine the "adequate dosage" of treatment for individuals receiving ECT. Finally, it appears that changes in neuroendocrine tests during ECT may be of great

assistance in the identification of patients with a high likelihood of relapse. There is a need for prospective studies to clarify these questions. The clinician using ECT may then be able to use objective criteria to support decisions on patient selection, duration of ECT course, and the need for continuation treatment.

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Hemispheric Asymmetry in Affective Disorders

Henry A. Nasrallah, M.D.[1]

Introduction

Over the past 30 years, significant advances have been made in the understanding of the cerebral hemispheric and interhemispheric functions in the human brain. In contrast to previous notions that the two cerebral hemispheres were duplicate structures with one dominant/major (usually the left) and another nondominant/minor (usually the right) hemisphere, research over the

[1]Department of Psychiatry, University of Iowa College of Medicine and VA Medical Center, Iowa City, IA

Address Correspondence to:
Henry A. Nasrallah, M.D., Chief, Psychiatry Service, VA Medical Center, Iowa City, IA 52240.

past three decades has established that the two cerebral hemispheres are structurally and functionally asymmetrical, and that both have to be fully integrated to produce optimal mental activity.

The quantum leap in the understanding of hemispheric asymmetry was the product of the pioneering work of Sperry and others into the split brain of animals (Myers & Sperry, 1953; Sperry, Stamm, & Miner, 1956; Sperry, 1961) and humans (Gazzaniga, 1970) showing that the surgically separated hemispheres contain two independent spheres of consciousness, with different motor, perceptual, cognitive, conative, and emotive functions. The separated cerebral hemispheres can be trained to concurrently perform contradictory tasks, and cerebral dominance for a certain task (i.e., laterality) can be experimentally shifted from one hemisphere to the other. In the human brain, the left hemisphere is usually more specialized for verbal, analytical, logical, and propositional tasks while the right hemisphere is more specialized for spatial, synthetic, intuitive, and oppositional tasks. The monumental studies of split-brain patients have indeed revolutionized the scientific and philosophical conceptualization of brain, mind, and the unity of conscious awareness (Sperry, 1968; Puccetti, 1973; Sperry, 1977; LeDoux, Wilson, & Gazzaniga, 1977).

Inevitably, the new knowledge of the cerebral hemispheric asymmetry of function triggered novel areas of psychiatric research which over the past decade has created an impressive body of evidence linking psychopathology with normal and abnormal cerebral lateralization (Gruzelier & Flor-Henry, 1979). Laterality shifts have been found in psychosis (Wexler & Heninger, 1979) and have been shown to be related to many factors frequently associated with psychiatric illness such as stress (Tucker, Roth, Arneson, & Buckingham, 1977), alcohol ingestion (Chandler & Parsons, 1977), sleep (Goldstein, Stoltzfus, & Gardocki, 1972), hypnosis (Frumkin, Ripley, & Cox, 1978), orgasm (Cohen, Rosen, & Goldstein, 1976), psychotomimetic drugs (Goldstein & Stoltzfus, 1973), and neuroleptics (Serafetinides, 1972).

Most of the research into hemispheric asymmetries in psychiatric illness has focused on the major psychoses such as schizophrenia and affective disorders. The literature has tended to suggest that schizophrenia is associated with left hemispheric as well as interhemispheric dysfunction (Newlin, Carpenter, & Golden, 1981; Nasrallah, in press). In this paper, a selective review of the literature on cerebral laterality in affective disorders will be presented, with a special reference to implications for electroconvulsive therapy (ECT) research.

Hemispheric Asymmetries in Affective Disorders

Unilateral brain lesions: The clinical presentations of patients with neurological lesions in the right or left cerebral hemisphere provided the first clue of hemispheric asymmetry for affect. Babinski (1914) noted that patients with right hemispheric lesions behaved indifferently to the contralateral sensory-motor deficits. Goldstein (1939) noted that left hemispheric lesions were associated with a catastrophic reaction, whereas right hemispheric lesions were associated with indifference. Gainotti (1972) observed that the emotional and psychiatric symptoms accompanying a brain lesion depend on the side of the lesion.

Nasrallah and McChesney (1981) reported that tumors of the corpus callosum were significantly more likely to manifest clinical signs and symptoms of depression than tumors in either cerebral hemispheres. They suggested that interruption of interhemispheric interaction may be associated with affective symptoms.

Temporal lobe epilepsy: In a study of psychoses associated with temporal lobe epilepsy, Flor-Henry (1969) stated that left temporal lobe foci are more likely to be associated with a schizophrenia-like psychosis, while the right hemispheric foci are more likely to be associated with affective psychosis. Bear and Fedio (1977) reported that patients with right temporal lobe epilepsy had emotional tendencies and denied depression even when they appeared to have it, while patients with left temporal lobe foci had ideational traits and dyssocial behavior, and reported more depression even when they did not have it. They suggested that their findings indicate a hemispheric asymmetry for the expression of affect.

Intracarotid amytal effects: Terzian and Cecotto (1959) reported a differential response of

the two cerebral hemispheres to intracarotid sodium amytal injections with "depressive-catastrophic" reaction following the inactivation of the right hemisphere. These findings were replicated (Rossi & Rosadini, 1967), except in patients with diffuse brain damage (Alema, Rosadini, & Rossi, 1961), and not replicated by Milner (1967).

Hommes and Panhuysen (1971) gave unilateral intracarotid amytal to patients hospitalized for depression, and found that more dysphasia occurred with right carotid amytal, and the severity of depression correlated negatively with dominance for speech in the left hemisphere, suggesting that left hemispheric dominance is reduced in depression. Elevation of mood was noted with injections on either side to varying extents, but depressive reactions were difficult to ascertain against the background of preexisting clinical depression.

ECT and laterality: A large literature appeared during the past 15 years suggesting that ECT applied only to the right hemisphere is as effective as bilateral ECT for the treatment of depression, but that ECT to the left hemisphere only was significantly less effective than bilateral or right hemispheric ECT (Halliday, Davison, Brown, & Kreeger, 1968; Abrams & DeVito, 1969; Cronin, Bodley, Potts, Matgher, Gardner, & Tobin, 1970; Costello, Belton, Abra, & Dunn, 1970) which has led to suggestions that depression may be associated with right hemispheric dysfunction. Deglin and Nikolaenko (1975) found more dysphoric reactions following left ECT and more euphoric reactions following right ECT and concluded that the left hemisphere plays a major role in the regulation of mood.

Kronfol, Hamsher, Digre, and Waziri (1978) reported that before treatment with ECT, depressed patients had more abnormalities in neuropsychological testing of right hemisphere functions compared to the left, and that after ECT (whether unilateral right or left) the right but not the left hemispheric functions were improved.

Nasrallah, McCalley-Whitters, and Keelor (submitted for publication) tested depressed patients for sensory and motoric lateralization before and after ECT to examine the effect of ECT on hemispheric dominance. All patients experienced shifts in either sensory or motor lateralization, but with equal frequency towards left and right hemispheric dominance.

EEG asymmetry: Using power spectrum EEG, Flor-Henry (1976) showed that schizophrenia is associated with left temporal EEG abnormalities, while affective illness is associated with right temporal abnormalities. Urstad (1979) found higher alpha activity on the left compared to the right temporal region in a group of schizophrenic and depressed patients, while the control group had a reverse pattern. After treatment, the depressed patients showed normal alpha predominance over the right hemisphere.

Abrams and Taylor (1979) examined 132 rigorously diagnosed patients with affective disorder and compared them to 27 schizophrenic patients. They found that the schizophrenic patients had a higher rate of abnormal EEG, particularly temporal slowing, whereas the affective group had more parieto-occipital abnormalities. They also noted that EEG abnormalities were lateralized, with predominantly left hemispheric abnormalities in schizophrenia and predominantly right hemispheric abnormalities in the affective group.

Skin conductance: Brain damage has been found to be associated with decreased skin conductance on the side ipsilateral to the lesion (Sourek, 1965). Gruzelier and Venables (1974) found decreased skin conductance on the right side in depressed patients and concluded that there is right hemispheric dysfunction in depression. Myslobodsky and Horesh (1978) reached the same conclusion, but with the findings of high conductance on the left side in depressed patients, which they interpret as evidence of contralateral brain dysfunction in the right hemisphere.

Dichotic listening: Dichotic listening has been shown to be a reliable method of indicating which cerebral hemisphere is dominant for language functions (Kimura, 1967). Yozawitz, Bruder, Sutton, et al. (1979), using verbal and nonverbal auditory stimuli, found that ear asymmetry of affectively ill patients was similar to patients with right temporal lobe lesions. They also found that neuroleptics worsen this asymmetry in affective patients but normalize it in schizophrenic patients.

Wexler and Heninger (1979) reported that the normal dichotic asymmetry diminished in both schizophrenic and depressed patients when the psychopathology was high and was restored when

patients improved. They concluded that psychotic illness is associated with a shift in laterality from left to right.

Bruder and Yozawitz (1979) also found that dichotic asymmetry in depression is consistent with right hemispheric dysfunction. Caudry and Kirk (1979) found schizophrenic patients to have a right ear advantage, while depressed patients have a left ear advantage. They concluded that depressives have a higher tendency for speech to be located in the right hemisphere.

Lateral eye movements: Conjugate lateral eye movements have been hypothesized to reflect activation of the cerebral hemisphere contralateral to the direction of gaze (Bakan, 1971). Verbal tasks have been shown to activate the left cerebral hemisphere, and spatial and emotional tasks preferentially activate the right cerebral hemisphere (Kinsbourne, 1972; Schwartz, Davidson, & Maer, 1975).

Schweitzer (1979) reported that depressed patients initiated reflective tasks more often in the right hemisphere. Myslobodsky and Horesh (1978) found depressed patients to look more often to the left for various tasks, and concluded that there may be right hemispheric overactivity in depression.

Motoric lateralization: Handedness is a crude measure of cerebral dominance for motoric laterality, with right handedness indicating left hemisphere dominance, and left handedness or ambidexterity reflecting right hemisphere dominance, in some cases due to early brain insult and left cerebral impairment (Satz, 1972).

Left handedness has been reported to be high in schizophrenia (Dvirskii, 1976; Gur, 1977; Nasrallah, Schroeder, Keelor, & McCalley-Whitters, 1981), particularly the paranoid subtype (Nasrallah, Kuperman, McCalley-Whitters, & Keelor, 1981). An increased frequency of left handedness in affective disorders has been reported by some investigators (Lishman & McMeekan, 1976; Flor-Henry, 1979) but not by others (Fleminger, Dalton, & Standage, 1977; Nasrallah & McCalley-Whitters, in press).

Neuroanatomical measurements: Rosenthal and Bigelow (1972) reported an increase in the thickness of the corpus callosum (the largest interhemispheric commissure) in postmortem brains of chronic schizophrenic patients. This has been widely interpreted as possible evidence for interhemispheric dysfunction in schizophrenia.

In the only other study of corpus callosum thickness in schizophrenia (Nasrallah, Bigelow, Rauscher, & Wyatt, 1979), brains of patients with bipolar affective disorder were also studied. The mean corpus callosum thickness in the affective group was almost identical to that of the late onset (paranoid) schizophrenic group, but almost significantly less ($p < .08$) than the early onset (nonparanoid) schizophrenic group. Histological studies of the corpus callosum in affective disorders are also similar to the late onset schizophrenic group (Nasrallah, McCalley-Whitters, Bigelow, & Rauscher, 1982).

Positron emission tomography (PET): Very recent studies of brain glucose metabolism using PET scans suggest that in contrast to the hypofrontal pattern seen in schizophrenic patients, patients with bipolar disorder have a hyperfrontal pattern during the manic phase. Asymmetry was also noted in schizophrenic patients (more metabolism in the right hemisphere) but data are not yet available on affectively ill patients (Farkas, 1980).

Discussion

The above review reflects the various lines of evidence for hemispheric asymmetry in affective illness. Although some form of right hemispheric dysfunction is the leading model for understanding hemispheric asymmetry of function in affective disorders, more evidence is needed to confirm that hypothesis and the specific nature of the hemispheric dysfunction in affective illness has to be defined. Many of the studies in this area of research suffer from methodological flaws that limit the reliability and validity of the results. Perhaps the greatest source of error is diagnostic accuracy, particularly in light of the heterogeneity of affective disorders, and the overlap with the schizophrenias. Almost all the studies of laterality did not use accepted diagnostic criteria such as the Diagnostic and Statistical Manual-III (DSM-III). The measurement of laterality is another area that requires further reliability and validity research (Colbourn, 1979).

The critical research issue in the area of hemisphere asymmetry of function in affective illness is therefore the establishment of whether one

of the cerebral hemispheres is differentially involved in affective illness and, if so, how. The proper strategy for answering this question should involve multiple measures of laterality in rigorously defined drug-free populations of affectively ill patients diagnosed by specific and reliable criteria.

ECT research can provide an excellent avenue for the study of hemispheric asymmetries in affective illness. ECT is an effective somatic treatment which is more easily quantifiable compared to pharmacological treatments. It also offers the distinct advantage and flexibility of being administered to either cerebral hemisphere or to both, whereas drugs are given systemically and therefore cannot be targeted to one part of the brain only. Thus, ECT offers a unique therapeutic and research strategy for the investigation of hemispheric dysfunction in affective illness. Patients could be assessed prior to treatment for both psychopathology and neuropsychological deficit as well as for measures of laterality such as EEG, dichotic listening, tachistoscopy, skin conductance and motoric preference. Repeat evaluation after unilateral ECT treatment to one hemisphere would then provide valuable data as to any dysfunction in either hemisphere, and to the concomitant laterality changes (if any) with therapeutic response.

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The Relative Efficacy of Unilateral Nondominant and Bilateral Stimulation

Charles A. Welch, M.D.[1]

Unilateral nondominant electrode placement offers a marked reduction in adverse cognitive effects when compared to bilateral placement. In spite of this clear finding, bilateral placement remains the standard technique in the United States, and the 1976 APA Task Force on electroconvulsive therapy (ECT) found that 75% of survey respondents used bilateral electrode placement exclusively, presumably in the belief that it is more effective than the unilateral technique. The same is true in the United Kingdom. Over 35 different studies have compared the efficacy of unilateral and bilateral placement, but the results have been contradictory. Most investigators find equal efficacy for the two methods, and a few studies show one or the other to be superior. This disparity in findings has persisted to the present in spite of increasingly rigorous research designs. Because of the reduced morbidity associated with unilateral nondominant placement, it remains a pressing research priority to ascertain whether unilateral nondominant and bilateral placement are equally effective.

In a major review of this literature, d'Elia and Raotma (1975) examined 29 studies of this question published from 1962 to 1973. They divided the studies into five groups according to methodological criteria (random assignment, blind comparison, simultaneous controls, homogenous diagnostic groups, and open number of ECT treatments). They observed that the more rigorous the methodology, the more equivalent the efficacy of unilateral nondominant and bilateral ECT appear to be, and that of the five followup studies from 1 to 12 months, all found equal efficacy. They concluded, "The review of studies performed under adequate methodological conditions shows that nondominant ECT has the same antidepressive effect as bilateral ECT. This is in agreement with our knowledge that the antidepressive factor of ECT is bound to the seizure. Nondominant ECT has the advantage of a much lower frequency and intensity of side effects. In endogenous depression nondominant ECT should be the treatment of choice."

They speculated that one reason for the frequent finding of less efficacy with unilateral nondominant treatment may have been more frequent missed seizures with this technique than with bilateral placement.

Since this review, there have been five published comparison studies, and there are two in press. They have yeilded differing results.

Abrams and Taylor (1976) compared bilateral and simultaneous unilateral dominant and unilateral nondominant stimulation. They used random assignment, and a blind rater assessed improvement with the Hamilton Depression Scale 5 hours after the sixth treatment. Sine-wave stimulation was used throughout and there was no seizure monitoring. Bilateral ECT was found to be significantly more effective than simultaneous unilateral dominant–unilateral nondominant. The authors concluded, "The therapeutic differences we observed between our two treatment methods might therefore be explained by the different degree of diencephalic stimulation, the degree of frontal lobe stimulation, or both."

Although scientifically very interesting, this study is not a direct comparison of unilateral nondominant and bilateral ECT, and does not specifically address the question at hand.

Reichert, Benjamin, Keegan, and Marjerrison (1976) compared bilateral and unilateral nondominant ECT in a study of 50 patients. They employed a sinusoidal wave form but no seizure monitoring, although they stated that "All patients exhibited full tonic-clonic seizures." Blind raters assessed patients with the 17-scale Brief Psychiatric Rating Scale (BPRS) prior to treatment and 1 and 3 weeks after the last ECT. In addition, patients completed the Hildreth Mood and Attitude Scale, a subjective rating instrument, prior to treatment and 1 day after the third, fourth, fifth, sixth, and last treatments, and at 1 and 3 weeks after the last treatment. An open number of ECT were given based on clinical judgment. The authors found that there was no significant difference between the two groups on the BPRS ratings at 1 or 3 weeks. However, the bilateral group was significantly more improved subjectively at all points in time except the final

[1]Somatic Therapies Consultation Service, Massachusetts General Hospital, Boston, MA 02114.

rating at 3 weeks posttreatment, at which time there was no difference between the groups. They also found a 26% 1-month relapse rate with the unilateral group but only a 3% 1-month relapse rate with the bilateral group.

Heshe, Roder, and Theilgaard (1978), in a study of 51 patients, used random assignment and double-blind design in a comparison of bilateral and unilateral nondominant ECT. A sine-wave stimulus was used without seizure monitoring. The Hamilton Depression Scale was given pre-ECT and then 1 week and 3 months after the last treatment. The bilateral group was found to be slightly but significantly more improved at 1 week after treatment, but the difference disappeared at 3 months followup.

Weeks, Freeman, and Kendell (1980) studied 102 patients, comparing bitemporal with unilateral nondominant ECT. Sine-wave stimulus was used but there was no seizure monitoring. The number of ECT was open with a mean of 7.4 in the unilateral group and 7.2 in the bilateral group. Assignment was nonrandom, but blind raters assessed efficacy with the Hamilton Depression Scale pre-ECT and then at 1 week, 4 months, and 7 months after the last ECT. There were no significant differences in the degree of improvement at any of the assessment points. The authors performed extensive cognitive testing which confirmed prior findings that unilateral nondominant ECT causes very little cognitive impairment even short term, and markedly less impairment than bilateral ECT.

Fraser and Glass (1980), in a study of 29 elderly depressed patients with a mean age of 73, compared bitemporal and unilateral nondominant ECT. A unidirectional chopped sine-wave stimulus was used without seizure monitoring. Patients were randomly assigned and blind raters assessed improvement with the Hamilton Depression Scale pre-ECT, 24 hours after the fifth treatment, and 3 weeks after the last treatment. The number of treatments was free with a mean of 6.1 in the unilateral groups and 6.9 in the bilateral groups. The mean pre-ECT Hamilton score was 46 for both cells. No significant differences were found on Hamilton Depression Scales at either of the post-ECT test intervals. Assessment of cognitive side effects showed no correlation between severity of side effects and outcome.

Abrams, Taylor, Faber, et al. (in press), in a randomly assigned, double-blind study of 51 patients, compared bitemporal and unilateral nondominant ECT. Stimulation was delivered by sine-wave apparatus, and seizures were monitored with an oscilloscope. Improvement was assessed by the Hamilton Depression Scale after the sixth treatment. The total number of treatments was free, with a mean of 6.3 in the bilateral group and 9.1 in the unilateral group. The bilateral group showed 81.1% improvement on the Hamilton Depression Scale after six ECTs, while the unilateral group showed only a 55.5% improvement ($p = .004$), a finding which was independent of age, sex, pretreatment severity of illness, or sedative drug administration. After 10 treatments, the primary clinician, who was a blind rater, was free to switch to the alternate electrode placement if the series was felt to be ineffective. Seven unilateral patients were switched to bilateral, while none of the bilateral group was switched to unilateral ($p = .008$). Finally, no patient in the bilateral group received more than nine ECTs, compared with 10 patients in the unilateral group ($p = .0007$).

Welch, Weiner, Weir, et al. (1982) randomly assigned 59 patients to one of four modalities: unilateral nondominant sine, unilateral nondominant brief pulse, bilateral sine, and bilateral brief pulse. Stimulation was delivered by either a bidirectional sine-wave apparatus or a bidirectional brief-pulse apparatus, both at threshold levels of current. Seizures were monitored with either EEG or occlusion of ipsilateral upper extremity circulation. Improvement was measured by the difference between blindly obtained Hamilton Depression Scale ratings pre-ECT and 48 hours after the last ECT. The total number of treatments given was determined by a nonblind clinician and was 8.1 for the unilateral group and 7.3 for the bilateral group, a nonsignificant difference. The mean reduction in Hamilton Depression Scale was 35.1 for the unilateral group and 25.1 for the bilateral group ($p = .03$). No significant effect of waveform, age, sex, or number of treatments could be found. The authors speculated that the bilateral group may have appeared more depressed at 48 hours after the last treatment because of greater side effects associated with that treatment, and that the treatments were in fact probably equally efficacious.

Conclusion

The disparity between the findings of various investigators is difficult to explain. The most likely source of the difference in results rests in the failure of most investigators to use fastidious seizure monitoring. It has been suggested by Ottosson (1960) and asserted by subsequent investigators that the grand mal seizure itself is the therapeutic component of the treatment, and that the method of induction appears unrelated to efficacy as long as a generalized grand mal seizure is elicited. It is also established that unilateral or incomplete seizures are ineffective (Ulett, Gleser, Caldwell, & Smith, 1954; Fink, Kahn, & Green, 1958; Chatrian & Petersen, 1960) perhaps because they fail to recruit diencephalic centers. However, such incomplete seizures occur more frequently with unilateral than with bilateral stimulation (Lancaster, Steinert, & Front, 1958; Halliday, Davison, Browne, & Kreeger, 1968). In the absence of seizure monitoring, these ineffective seizures cannot be reliably identified and may be the cause of the frequent feeling that unilateral stimulation is less effective.

Another source of bias may be the different patient populations involved in these trials. For instance, the most recent work by Abrams et al. (in press) was done in a mostly male veterans' hospital population, while the population studied by Welch et al. (in press) was a mixture of general hospital and veterans' hospital patients.

The only firm conclusion that can be drawn is that further research is indicated to resolve the question of relative efficacy of unilateral nondominant and bilateral electrode placement. At this point it would appear that the only way to resolve it would be a large multicenter, randomly assigned, double-blind comparison, which simultaneously controls for side effects. Both short- and long-term assessment of severity of depression would be indicated.

Most important, however, is the monitoring of the seizure. Seizure monitoring should be done simultaneously by occlusion of arterial flow in the ipsilateral arm, with a blood pressure cuff, but also by a two-lead electroencephalograph (EEG) monitor. The EEG provides an accurate measure of seizure length, but occasionally fails to distinguish between partial and complete seizures, which are identical in appearance on a two-lead tracing. The occlusion of ipsilateral circulation provides a reliable check against this error, since partial seizures do not generally produce convulsive activity in the ipsilateral arm.

Although the research design outlined above is time consuming and cumbersome, the well-documented morbidity associated with the use of bilateral ECT warrants such a fastidiously controlled study to ascertain whether it is indeed more effective than unilateral nondominant ECT and, if so, in which patients.

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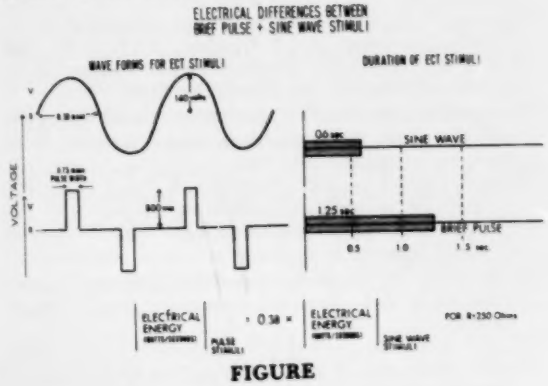
The Role of Stimulus Waveform In Therapeutic and Adverse Effects of ECT

Richard D. Weiner, M.D., Ph.D.[1]

Introduction

In electroconvulsive therapy (ECT), a seizure is produced by the application of a train of stereotypic electrical stimuli known as "waveforms." Although diverse types of stimulus waveforms have been used over the years, this brief review will consider just two, the sine wave and the pulse. These are the major waveform types utilized at the present time in the U.S.A., and they are representative of both ends of the waveform spectrum.

The sine wave stimulus (*see* Figure) is an oscillating pattern which is repeated 60 times a second (60 Hz). It is the same type of waveform which comes out of the wall socket, and for this reason not only was it the first stimulus waveform to be used with ECT, but also it is the one which remains the most popular stimulus waveform in the U.S.A. Adjustable parameters for the sine wave stimulus include voltage or current, and duration. The Figure shows typical initial parameter values for the use of the Medcraft B-24 (Hittman Corp.) sine wave ECT device (140 volts rms, 0.6 seconds' duration). For a patient resistance of 250 ohms, this stimulus will deliver 47 joules of electrical energy.



FIGURE

The pulse stimulus (*see* Figure) was first used with ECT in the early 1940s (Liberson, 1948), to produce seizures with a smaller amount of electrical energy, and thereby hopefully less adverse central nervous system (CNS) effects. The range of potential parameters with pulse ECT consists of voltage or current, duration, pulse width, and pulses per second (which reflects pulse spacing). The Figure shows typical initial parameter values for the MECTA (MECTA Corp.) pulse ECT device (800 ma current, 1.25 seconds' duration, 0.75 msec pulse width, and 60 pulse pairs per second). Again for a patient impedance of 250 ohms, this stimulus will deliver 18 joules of electrical energy, 38% of that described above for the sine wave stimulus. It should be noted that the energy per phase is considerably lower with the pulse stimulus, and that a longer stimulus duration is therefore generally necessary in order to provide the extent of neuronal depolarization necessary to initiate the seizure.

Therapeutic Correlates of Stimulus Waveform

The initial claims for the efficacy of pulse vs. sine wave ECT were that the two were equivalent (e.g., Liberson, 1948), although the research methodology was far from adequate. More recently, two prospective studies have demonstrated no significant therapeutic difference between sine wave and pulse stimuli (Weaver, Ives, Williams, & Nies, 1977; Welch, Weiner, Weir, Cahill, Rogers, Davidson, & Mandel, 1982). Others have suggested that the particular combination of pulse unilateral ECT may be less effective than other combinations (Lambourne & Gill, 1978; Price, 1981). Although such a phenomenon was not observed by either Weaver et al. (1977) or Welch et al. (1982), it remains possible that there may be a relatively small subgroup of patients who do not respond as well to unilateral ECT, whether given by pulse or by sine wave. At the same time, however, it should be made clear that the technique of unilateral ECT is considerably more difficult than with bilateral ECT, and that studies which have controlled for this have found little therapeutic difference between the two types of electrode placement (Weiner, 1980).

[1]Durham Veterans' Administration Medical Center and the Department of Psychiatry, Duke University Medical Center, Durham, NC 27710.

The role of pulse width in the diminishing of energy per phase has already been alluded to above. While shortening pulse width allows for more efficient seizure induction, it appears that ultrabrief pulses (pulse width less than 0.5 msec) may be associated with less complete, and thereby less effective, seizures (e.g., Cronholm & Ottosson, 1963).

The Effects of Stimulus Waveform Upon Adverse Effects

Early studies which compared pulse and sine wave stimuli with respect to adverse effects reported that, with the former, patients woke up earlier and demonstrated less confusion and amnesia (e.g., Liberson, 1948). Despite these claims, however, the methodology of these studies was inadequate in a number of ways, particularly in the use of concurrent differences in electrode placement between treatment groups, such that the observed advantage for pulse stimuli could actually have been due to the use of unilateral electrode placement.

More recently, Valentine, Keddie, and Dunne (1968) found less amnestic changes with pulse stimuli, but measurements were only made during the immediate postictal period and are therefore not applicable to interictal, and particularly to persistent, effects. Goldstein, Filskov, Weaver, and Ives (1977), using a comprehensive neuropsychological assessment battery, found no such difference 1 day following a course of ECT. Finally, Weiner, Rogers, Davidson, and Miller (1982), in a preliminary report, have described similar findings 2 days following a course of ECT, using sensitive measures of memory assessment, although a nonsignificant trend ($p \cong 0.08$) favoring the pulse stimulus was present. Electroencephalographically, the less intense seizures produced by pulse stimuli do, however, appear associated with less slowing 2 days after a course of ECT, based again on preliminary data (Weiner et al., 1982).

Summary and Recommendations for Future Research Investigations

In summary, the relative efficacy and safety of pulse stimuli with respect to sine wave stimuli is an issue deserving further study. While the two stimulus waveforms do appear to be roughly equivalent in terms of efficacy and memory effects, present studies have not been sufficient to delineate possible small differences, and there is some indication that waveform may have an effect upon acute electrophysiologic morbidity. Specific research questions for the future include:

1) Are there some patients who are more likely to respond to sine wave than to pulse stimuli, particularly in the case of unilateral electrode placement?
2) What are the specific roles of amplitude, pulse width, pulse separation, and stimulus duration in the production of effective seizures with pulse stimuli?
3) To what degree are adverse CNS effects less with pulse stimuli?

Answers to these questions will help to more adequately delineate the role of both types of stimuli in the clinical practice of ECT.

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ECT and Tricyclic Antidepressants in the Treatment of Endogenous Depression

Richard Abrams, M.D.[1]

It is an axiom among psychopharmacologists that rigorous experimental methods are required to demonstrate the efficacy of a new drug or its advantages over an old one. A prospective design, random assignment to treatment groups, and blind assessment of outcome are prerequisites in such studies. Other requirements include specified diagnostic criteria, objective outcome measures, and appropriate statistical analysis of the outcome data. Nothing less can ever suffice to demonstrate the absolute or relative efficacy of any treatment, and electroconvulsive therapy (ECT) is no exception. Considering that ECT and tricyclic antidepressants (TCAs) have coexisted for almost a quarter-century, and that endogenous depression is the primary indication for each treatment, it would be reasonable to expect a substantial number of comparisons of the two methods in this target population, employing such rigorous methodology. Such is not the case. There are, in fact, very few data to support the oft-heard comment that ECT is superior to TCA in the treatment of endogenous depression. Only two studies satisfied the minimal design criteria specified above, and one of the studies is seriously flawed by inadequate sample size.

The first study is that of Wilson and associates (1963) who conducted a two-phase trial in a sample of women hospitalized for manic-depressive illness, depressed type, involutional depression, or depressive reaction. In the first phase, patients were randomly assigned to four treatment groups of which two (six patients each) were ECT + placebo and placebo + imipramine (mean dose = 180 mg/day, range = 150 to 220 mg/day). Hamilton Rating Scale Scores obtained by blind raters after 5 weeks showed a change (improvement) score of 22.3 ± 1.6 for the ECT group, compared with only 11.7 ± 4.5 for the imipramine group ($t = 5.44$, $p < .005$). Fourteen new patients were then added to the study, four to receive ECT and 10 to receive imipramine at a higher dose (mean = 258 mg/day, range = 215 to 270 mg/day). This time, the improvement score after 5 weeks for the imipramine group was 25.1 ± 1.8, significantly greater than that of 22.5 ± 1.6 for the total of 10 ECT patients ($t = 3.41$, $p < .005$). (The authors erroneously concluded that the two treatments in this phase are "identical," but fortunately provide means and standard deviations for the inquisitive reader.) A major problem with this study is its very small sample size.

The second study is that reported to the Medical Research Council of Great Britain by its Clinical Psychiatry Committee (1965) Two-hundred sixty-nine patients with endogenous depression were randomly assigned to four different treatment groups. One group received four to eight ECT treatments ($N=65$) and another received imipramine ($N=63$) at a dose of 100 to 200 mg/day (mean = 193 mg/day). Fifty-eight patients in each group completed the first 4 weeks of treatment, at which time blind assessments on a 15-item depression rating form showed 71% of the ECT group recovered or markedly improved, compared with 52% of the imipramine group ($X = 4.99$, $p < .05$).

Thus, of two methodologically adequate studies, one shows a clear advantage for ECT over moderate-dose imipramine, and one shows a slight advantage for high-dose imipramine over ECT. The remainder of the ECT vs. TCA studies reviewed (Alexander, 1972; Angst, Varga, & Shepherd, 1967; Avery & Winokur, 1976; Bratfos & Haug, 1965; Bruce, Crone, Fitzpatrick, et al., 1960; Coryell, 1978; Fahy, Imlah, & Harrington, 1963; Greenblatt, Grosser, & Wechsler, 1962; Hutchinson & Smedberg, 1963; Kristiansen, 1961; McDonald, Perkins, Marjerrison, & Podilsky, 1966; Ravn, 1966; Robin & Harris, 1962; Wittenborn, Plante, Burgess, & Maurer, 1962) have the methodological problems detailed in the Table.

The study by Greenblatt et al. (1962) exemplifies the problem presented by well-known studies which must nonetheless be rejected as methodologically inadequate. The study employed random assignment, blind evaluations, and adequate drug dosages. It also correctly concluded that ECT was superior to imipramine in the total sample of 281 patients. Unfortunately, the sample was diagnostically heterogeneous and

[1]Department of Psychiatry, University of Health Sciences/The Chicago Medical School, North Chicago, IL 60064.

Table

Methodological Problems of ECT vs. TCA Studies

Study	Retrospective, Chart Review	Faulty Data Analysis	Non-Blind Evaluation	Non-Endogenous Depressives	Unstated Drug Dosage	Unstated Number of ECT	Unstated Outcome Criteria or Method
Bruce et al., 1960			+				+
Kristiansen, 1961	+						
Wittenborn et al., 1962				+	+	+	
Robin and Harris, 1962		+			+	+	
Hutchinson and Smedberg, 1962		+					
Fahy et al., 1963			+				
Greenblatt et al., 1964		+					
Bratfos and Haug, 1965	+						
McDonald et al., 1966			+				
Ravn, 1966	+						
Angst et al., 1967	+						
Alexander et al., 1972	–						
Avery and Winokur, 1977	+						
Coryell, 1978	+						

included 51 psychoneurotic depressives, 60 schizophrenics with depression, and 44 patients diagnosed only as "other." Thus, more than half the sample was nonendogenous, and cannot be combined for analysis. They do present a table displaying global improvement rates separately for each diagnostic subgroup, including the two presumably endogenous categories of manic-depressive, depressed ($N=76$), and involutional psychosis ($N=50$), but no statistical analyses or significance levels are described and the table is presented in such a peculiar fashion that the reader is unable to conduct his own analysis. An unsupported statement appears in the text that (among 28 other comparisons) ECT was no better than imipramine in the manic-depressives but was more effective than imipramine in the involutionals. In view of the multiple significance tests performed, the latter conclusion is unwarranted.

There is an additional problem with the ECT vs. TCA literature. Recent data suggest that optimal TCA therapy requires plasma-level monitoring, and several investigators have reported a significant relationship between TCA plasma levels and clinical outcome (Glassman & Perel, 1978). The largest study is that of Glassman, Perel, Shostak, et al. (1977), who treated 42 nondelusional endogenous depressives with a fixed (mg/kg) dose of imipramine and related plasma levels of this drug to clinical response as measured by changes in depression rating scale scores. The proportion of imipramine-responders increased in a stepwise fashion and was 29% in the group with plasma levels <150 ng/ml, 64% at 150-225 ng/ml, and 93% in the patients with levels exceeding 225 ng/ml, a figure quite comparable to improvement rates obtained with ECT in other studies. This study is marred by the fact that the authors do not specify their precise criteria for defining "responders" and "nonresponders."

Nonetheless, the results of the Glassman et al. (1977) study suggest that a valid comparison of the effects of ECT and TCA requires plasma-level monitoring in order to provide optimal TCA therapy. The need for such a study is obvious and should take first priority in future assessments of the efficacy of ECT.

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Factors Affecting Outcome After Successful Electroconvulsive Therapy

Roger F. Haskett, M.B.B.S.[1]

Electroconvulsive therapy (ECT) is accepted as an effective treatment for certain acute psychiatric syndromes, particularly the major affective disorders. Unfortunately, a significant number of patients relapse within a few months of a successful course of ECT. When examining this observation, it is important to consider the natural history of these illnesses and some popular assumptions about the long-term effects of treatment. Major affective disorders are commonly episodic and have a high spontaneous remission rate. It is usually impossible, however, to predict the duration of an untreated episode or the length of time that would elapse before the appearance of another episode. Pharmacotherapy of major affective disorder appears to assume that treatment reverses the pathogenetic process responsible for the clinical syndrome, but that the unidentified primary pathology persists. Antidepressant medication is continued for 6-12 months after clinical remission to prevent reappearance of the episode. Although there is no objective criterion for determining the appropriate time to withdraw medication, clinicians frequently deal with the uncertainty by extending the duration of treatment. By comparison, a course of ECT cannot be prolonged without definite indications. The number of treatments given to an individual must be limited because of concerns that excessive ECT produces serious side effects on cognitive functioning. In addition, outpatient ECT has many practical difficulties. The combination of the need to use ECT sparingly, and the lack of criteria for determining the spontaneous endpoint of an episode, have led to great variation in the long-term management of patients with ECT.

In the absence of objective markers for the therapeutic effects of ECT, clinicians have adopted various arbitrary guidelines to determine the "optimal dosage" of ECT. The twofold aim is to produce a full remission of the acute psychopathology and a low relapse rate. These guidelines are usually empirical and in most cases

[1]Department of Psychiatry, University of Michigan, Ann Arbor, MI 48109.

inadequately tested by appropriately designed clinical studies. An inflexible number of treatments or duration of the course of ECT is sometimes prescribed without consideration for the clinical response of the patient. A frequently recommended practice consists of giving an additional two treatments after full remission of symptoms. Most commonly, clinicians are advised to treat until the psychopathology has resolved with the proviso that a certain minimum and maximum number of treatments are advised (American Psychiatric Association Task Force Report #14, 1978).

Clinical indications for followup treatment are more confusing than those dealing with treatment of the acute disorders. There appears to be little consensus on the risks of giving no continuation treatment, or the efficacy of specific medications or maintenance ECT in preventing relapse. Some clinicians believe that the characteristics of the original course of ECT significantly influence the relapse rate, whereas others suggest that outcome depends upon the use of prophylactic treatment and the natural history of the disorder.

A review of the literature does not provide the date to resolve these uncertainties. Interpretation of many reports is hindered by the use of different diagnostic systems and limitations in study design. Despite these constraints, there are several studies which provide some information on the outcome of successfully treated patients who have differing post-ECT interventions.

There are two reports which compare maintenance ECT with no treatment after recovery from the acute illness. Maintenance ECT was given on a varying schedule but no more than one treatment per month. The control or untreated groups consisted of patients who refused the offer of maintenance therapy. Geoghegan and Stevenson (1949) reported that 100% (13/13) of patients receiving maintenance ECT were well after 3 years and only 15% (2/13) relapsed in the subsequent 2 years (Stevenson & Geoghegan, 1951). By comparison, 100% (11/11) of patients who refused continuing treatment had relapsed within 3 years. All subjects had suffered two episodes in the 5 years prior to the study and "most" suffered from manic depressive illness. Karliner and Wehrheim (1965) offered a similar choice to 210 patients who had suffered a psychotic episode in the previous year which was successfully treated with ECT. After 6 years, only 12% of the patients treated with maintenance ECT had relapsed in contrast to 79% of the patients who had refused further ECT.

Although both studies showed a prophylactic effect for maintenance ECT, these results may not be replicated with randomly assigned patients recovering from their first psychiatric episode. The studies do demonstrate the difficulty in differentiating a relapse of the same episode of depression from the appearance of a new episode. The first study consisted of patients who already had evidence of frequently recurring episodes. The second study probably included many patients who had relapsed into the same episode after a temporary remission. The likelihood that these patients would suffer another episode within the followup period would depend upon the natural history of each patient's illness as well as the nature of the acute treatment. The effect of the patient's past history on his or her acceptance of maintenance therapy is also unlikely to be randomly distributed. The ability of maintenance ECT to sustain a remission during a single episode of illness, or prevent the occurrence of new episodes cannot be determined from these studies.

Thomas (1954) provided one of the earliest retrospective surveys of the long-term outcome of ECT. He examined the records of 307 patients and noted that 69% recovered or were much improved and another 28% were improved by a course of ECT. This author defined a "relapse" as a need for ECT within 4 weeks of original course of treatment. A "recurrence" occurred more than 4 weeks after treatment. Thomas found that 26% (81/307) of the patients "relapsed" and 91% (74/81) of these occurred by the 16th day post-treatment. Two hundred nineteen patients were followed for a further 12 months while receiving no somatic or pharmacological therapy. Fifty patients (23%) required readmission, further ECT, or committed suicide. Examination of the "recurrence" rates for these 219 patients revealed an interesting association. Sixteen percent (26/160) of the patients with an uneventful initial recovery had a "recurrence" during the subsequent year, whereas "recurrence" occurred in 41% (24/59) of the patients who "relapsed" during the initial course of treatment.

In one of the early attempts to find an objective

marker for an adequate course of ECT, Roth, Kay, Shaw, and Green (1956) studied pentothal-induced delta wave EEG activity. They reported that 29% (12/41) of patients in their study suffered a relapse during the first 12 weeks after treatment. Eleven of these relapsing patients had failed to meet their criterion of EEG change with ECT. Further development of this potential marker for an unfavorable prognosis following ECT does not appear to have occurred. Strain, Brunschwig, Duffy, Agle, Rosenbaum, and Bidder (1968) compared the outcome of depressed patients treated with unilateral or bilateral ECT. Thirty-seven percent (17/45) of patients receiving bilateral ECT and 34% (17/50) receiving unilateral ECT relapsed during the 12 months after treatment. These two reports are notable, since they were prospective studies and provide information on the relapse/recurrence rates in depressed patients given no further treatment after successful ECT.

There is one study (Barton, Melta, & Snaith, 1973) which examined the effect on relapse rate of an additional two ECT after symptomatic relief. Fifty patients completed a course of ECT with random assignment to one of two groups. The groups whose ECT ended as soon as depressive symptoms disappeared had a 50% (13/26) relapse rate during the subsequent 3 months. The group receiving two additional ECT had a 42% (10/24) relapse rate for a similar period. These rates were not significantly different. They did find, like Thomas (1954), that most of the relapses occurred within 2 weeks after treatment was completed.

There are three reports of the relapse rates in depressed patients assigned randomly to maintenance medication at the time of beginning ECT. Each study followed its patients for at least 6 months. Seager and Bird (1962) compared imipramine, 75 mg/day, with placebo. Seventeen percent (2/12) of the patients taking imipramine relapsed in the 6 months after ECT compared with 69% (11/16) of those taking placebo. A similar study (Imlah, Ryan, & Harrington, 1965) compared the efficacy of phenelzine, imipramine, and placebo. Placebo was discontinued at the time of discharge from hospital. Patients maintained on imipramine, 75 mg/day, or phenelzine, 45 mg/day, had a relapse rate of 22%, whereas those on no medication had a relapse rate of 51% during the 6-month period. The third study (Kay, Fahy, & Garside, 1970) compared the effects of diazepam, 4-12 mg/day, with amitriptyline, 50-150 mg/day. Forty-seven percent (24/51) of the former group relapsed, including three suicides, whereas only 24% (8/34) of those taking amitriptyline relapsed. These studies showed a high relapse rate for patients continued on a minor tranquilizer, placebo, or no medication and a much lower relapse rate if maintenance antidepressants were prescribed. The actual relapse rates for patients taking antidepressants may have been influenced by the fact that many individuals were taking lower dosages than are considered therapeutic today. The relapse rate for patients continued on lithium was also compared with patients taking tricyclics in a retrospective chart review (Perry & Tsuang, 1979). Both groups of patients had similar relapse rates of 20 and 21%, respectively. The three prospective medication studies were also designed to examine the belief that concurrent medication shortened the duration of, or decreased the number of treatments in, an acute course of ECT. In all cases, there was no significant difference in the course of ECT treatment when antidepressant medication was also given.

In a recent study, Coppen, Abou-Saleh, Milln, Bailey, Metcalfe, Burns, & Armond (1981) compared the efficacy of continuation therapy with lithium against placebo. The outcome measure used in this report was the mean number of weeks spent in a relapse during the followup period. During the first 6 months after ECT there was no significant difference between the group taking lithium and the group taking placebo. The group taking lithium, however, showed much less evidence of relapse during the second 6-month period (mean time in relapse of 0.2 weeks) compared with the patients taking placebo (5.6 weeks).

In conclusion, there is ample evidence that the relapse rate after a course of ECT is unacceptably high unless some form of maintenance antidepressant therapy is administered. There has been little progress in the identification of specific treatment practices, or objective markers of therapeutic effect, which can identify those patients with a good prognosis after ECT. The endpoint of a course of treatment remains arbitrary and there is no reliably demonstrated method for determining which patients require prophylactic treatment to

prevent relapse or recurrence.

It is possible that the characteristics of a course of ECT are no more able to influence the subsequent relapse rate than the initial treatment of melancholia with antidepressant medication. The tendency to relapse may be a function of the natural history, or subsequent duration of the episode, and may respond only to some form of continuation therapy. Studies which examine these questions must attempt to match patient groups for number of previous episodes, duration of current episode, and known recurrence rate. The development of biological markers which reflect the pathophysiology of the disorders and which can be used to monitor the therapeutic effect of ECT may enable the clinician to develop more objective guidelines for the administration of ECT. These markers may be neurophysiological or neurochemical, but perhaps the most hopeful developments have occurred with the use of neuroendocrine strategies. These are discussed in another section of this series.

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Electroencephalographic Correlates of ECT

Richard D. Weiner, M.D., Ph.D.[1]

Introduction

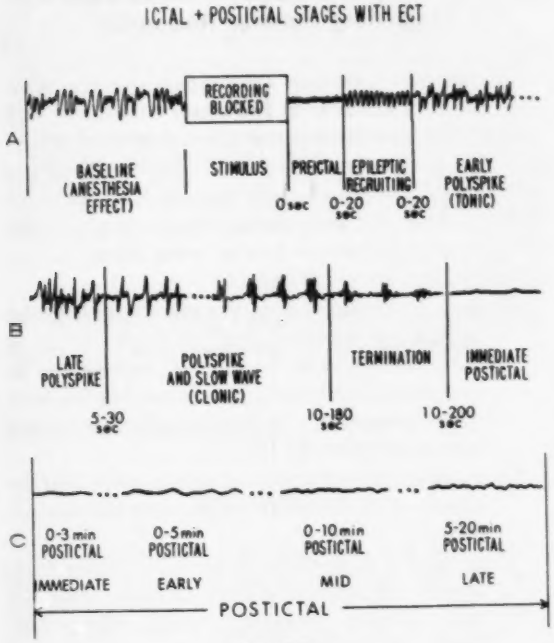
Electroconvulsive therapy (ECT) has a variety of effects upon the cerebral physiology, some of which may be correlated with therapeutic and adverse behavioral changes. From the early days of ECT, a routine test of cerebral function, the electroencephalogram (EEG), has proved to be a valuable means to observe and analyze the electrophysiologic correlates of these effects (Fleming, Golla, & Walter, 1939; Small, Small, & Milstein, 1978). The types of EEG changes seen with ECT can be subdivided chronologically into ictal, immediate postictal, interictal, and persistent categories.

The Ictal EEG

The prime function of the electrical stimulus used with ECT is to produce a generalized, major-motor type seizure. As such, the ictal EEG activity seen with ECT is strikingly similar to that observed with spontaneously occurring grand mal seizures. Electrically induced seizures may last anywhere from a few seconds to, rarely, many

[1]Durham Veteran's Administration Medical Center and the Department of Psychiatry, Duke University Medical Center, Durham, NC 27710.

minutes, with typical mean seizure durations ranging from 45 to 60 seconds. The ictal EEG can itself be subdivided, again on a temporal basis, into 5 phases: preictal, epileptic recruiting activity, polyspike activity, polyspike and slow wave activity, and termination, as shown in A and B of the Figure.



FIGURE

The preictal phase of the impending seizure is not commonly seen with ECT, since seizure onset is generally immediate, or is at least underway by the time EEG amplifiers have begun to unblock. When seen, this phase typically presents as a period of relative suppression (*see* A of the Figure).

The earliest ictal phase generally seen in the EEG is rhythmic 18-22 Hz beta activity, typically occurring in a bilaterally synchronous fashion and lasting from a fraction of a second to no more than a few seconds (*see* A of the Figure). This activity can be called the epileptic recruiting rhythm, in deference to the use of this term in epileptology. For unknown reasons, this phase often appears absent.

The recruiting rhythm gives way to a chaotic mixture of high amplitude polyspikes which mark the tonic and early clonic convulsive movements accompanying the seizure (*see* A and B of the Figure). This phase lasts from a few seconds to tens of seconds, with approximately 10-20 seconds being most common.

Often in a piecewise fashion, the polyspike activity begins to break up into a regular pattern of polyspike and slow wave discharges, which begin at a frequency of 4-6 Hz, eventually slowing to 1-2 Hz (*see* B of the Figure). This phase, which generally makes up the bulk of the seizure duration, may not always be as well formed as described above, however, and may present as a mixed polyspike and polyspike/slow-wave pattern. The clonic convulsive movements always end before, or at least concurrent with, the end of this phase.

The termination phase of the seizure may be quite varied, ranging from an abrupt dissipation, termed by Blachly and Gowing (1966) as the "fit switch," to a breaking up of the polyspike/slow-wave activity into an irregular mixture of polyspikes and slow waves of steadily diminishing amplitude which may last for up to 30 seconds or, rarely, more. A typical termination phase is shown schematically in B of the Figure.

As far as one can tell electroencephalographically, the seizure onset is generalized, suggesting an early diencephalic activation of corticoreticular pathways, yet there is some suggestive evidence for a local onset within the hemisphere of stimulation with unilateral ECT (Staton, Hass, & Brumback, 1981). In addition, there have been a number of reports of unilateral seizures with unilateral ECT, presumably in response to barely threshold stimuli. Another reported difference between unilateral and bilateral ECT is with respect to the magnitude of ictal activity, with both EEG amplitude and the intensity of clonic convulsive movements being asymmetric with unilateral ECT (Kriss, Halliday, Halliday, & Pratt, 1978). Although ictal EEG differences between sine wave and pulse stimulation have not been investigated, there have been reports that clonic movements may be less intense with the latter (Marshall & Dobbs, 1959). In general, seizure duration appears to be independent of electrode placement and stimulus waveform, except that with small interelectrode distances, seizures produced by sine wave unilateral stimulation may be somewhat abbreviated (Weiner, 1980a).

The Postictal EEG

Immediately postictally, there is some degree of suppression of EEG activity, much as there is following spontaneous grand mal seizures. The degree of suppression is quite variable, and is more prominant with longer seizures and with bilateral stimulation. With unilateral stimulation, the suppression is typically greater over the stimulated hemisphere, as one would expect given the higher amplitude of ipsilateral ictal EEG activity. In observing the postictal EEG in cases where little suppression occurs, one must take into account the fact that some degree of high amplitude mixed slow and fast activity may be present due to the effects of the barbiturate anesthesia and that this should not be confused with continuing ictal activity. By 10 to 15 minutes postictally, the EEG gradually returns to its baseline state, with an initial appearance of very slow delta activity followed by theta, alpha, and beta rhythms (*see* C of the Figure). This shift toward higher and more normal-appearing frequencies is most easily observed in records showing the greatest degree of suppression.

The Interical EEG

Interictally, the most prominent type of EEG finding is the presence of generalized slowing in the theta and delta ranges. This slowing may be either regular or irregular in morphology, is frequently accentuated by drowsiness and by hyperventilation, and is greater for both bilateral stimulation and with the use of sine wave stimuli (Weiner, Rogers, Davidson, & Miller, 1981). Though most often bilaterally synchronous, the slowing may occasionally be greater over the stimulated hemisphere with unilateral ECT. The degree of slowing varies quite a bit among individuals, but clearly increases with the number of treatments.

The Persistence of EEG Effects

The persistence of EEG changes, chiefly slowing following ECT, also appears to be quite variable. A recent review of this literature indicates that in most cases slowing disappears within the first month, and only rarely is it present past 3 months (Weiner, 1980b). The role of electrode placement and stimulus waveform in the persistence of EEG abnormalities is presently unclear.

Summary and Recommendations Regarding Further Research

In summary, despite a great deal of variability, the EEG correlates of ECT are relatively well described, and though occasional severe abnormalities may exist on an acute basis, the risk of permanent adverse changes appears low. Although much is known about these correlates, a number of pertinent questions in this area await further investigation for clarification:

1) In what fashion does the electrical stimulus induce the seizure?
2) To what degree is the seizure, and each of its structural components, responsible for both the therapeutic and the adverse effects associated with ECT?
3) Is the degree of postictal suppression and the speed of its recovery important therapeutically?
4) Is there a difference, in terms of either therapeutic or adverse effects, between patients who develop prominent EEG effects and those who do not?
5) What is the true incidence of long-lasting EEG abnormalities with ECT?
6) What roles do electrode placement, stimulus waveform, and stimulus intensity have in these EEG correlates, particularly in the persistence of EEG changes?

In attempting to answer these questions, we may arrive at a better understanding not only of how ECT works, but also in how it should be optimally used.

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Short- and Long-Term Cognitive Effects of ECT: Part I—Effects on Memory

Trevor R.P. Price, M.D.[1]

Introduction

In this article and the one that follows, the effects of electroconvulsive therapy (ECT) on various cognitive functions, both short- and long-term, will be reviewed. In the interest of simplification and clarity, they will be discussed in two separate sections: one dealing with the effects of ECT on memory function and the other with the effects of ECT on nonmemory-associated cognitive function. Obviously this is a heuristically useful though somewhat artificial distinction, since memory capacity is an important underlying component of at least some so-called nonmemory-associated cognitive functions.

In attempting to understand the effects of ECT on neuropsychological and cognitive functions, it is crucial to bear in mind that the diseases for which it is most frequently used, i.e., major depressive disorder and schizophrenia, may themselves cause significant changes in these functions. It is therefore important, but at the same time often difficult, in patients receiving ECT to separate out the extent to which observed cognitive changes are due to the treatment as opposed to the underlying disease. The article by Nasrallah in this series speaks to this issue in greater detail.

[1]Department of Psychiatry, Dartmouth Medical School, Hanover, NH 03755.

Memory Dysfunction Associated with Depression

Patients with depression may have impaired concentrating ability and experience difficulty in focusing attention (Wexler, 1980). Depression may also cause impaired memory function (Sternberg & Jarvik, 1976) of a particular type. It has been shown that short-term memory, which is dependent on registration, is impaired, while long-term memory, which is dependent on retention and recall, is not (Cronholm & Ottosson, 1961). Further, it is thought that impaired registration is a result of concentration and attention deficits, so-called "prograde effects" (Reichert, Benjamin, Neufeldt, & Marjerrison, 1976). It has been shown that when patients are treated, improvement in depression and short-term memory function are highly correlated and tend to be proportional in magnitude. In general, as will be detailed below, the memory impairments resulting from ECT tend to be just the reverse of those associated with depression. There may be uncertainty in some cases as to whether observed memory problems are due to depression or to the effects of ECT. Squire, Wetzel, and Slater (1979) have developed a self-rating instrument which may allow for differentiation between them. Using this scale, they showed that the patterns of memory complaints 1 week and 6 months post-bilateral ECT were qualitatively similar to each other, though quantitatively different, with the memory impairment at 1 week, as expected, being greater. In comparison to the pattern obtained before treatment, however, the two post-treatment scores differed both qualitatively and quantitatively, allowing for clear differentiation between them.

Methodological and Technical Issues

In reading the literature on the cognitive effects of ECT, one must be aware that much of the work

done in the past on the effects of ECT on memory and cognition has suffered from inadequate research methodology. There has been a great need evident in earlier studies, which has only in recent years begun to be met, for more standardized and sophisticated assessments of memory function (Harper & Wiens, 1975).

One must also bear in mind that conclusions regarding ECT's effect on memory depend to a great extent on how one measures memory function (Squire & Miller, 1974) and what one is measuring. Thus the experimental methodology employed; the sensory modality that is mediating memory, be it auditory, visual, or tactile; the content of the material administered, whether verbal or nonverbal; and whether one is measuring recognition, recall, relearning, or forgetting (the differences between immediate and delayed reproduction scores) are all important in interpreting and comparing the results of studies of the effects of ECT on memory function.

One should also be aware that while much is now known with a reasonably high degree of certainty about the effects of differential electrode placement on certain cognitive and memory functions, so-called laterality effects, their relationship to the type of stimulus waveform, and the frequency and intensity of stimuli and seizures have not thus far been adequately investigated.

The Effects of ECT on Memory Function

Memory impairment is a frequent and distressing, though for the most part, reversible, consequence of ECT. It occurs in a variety of forms which will be discussed below, and its nature and severity depend to an important degree on where and how the electric stimulus is delivered. While over the years this has been a subject of considerable debate, there is now widespread agreement that memory deficits are neither correlated with nor necessary for clinical improvement with ECT (Korin, Fink, & Kwalwasser, 1956; Fink, 1974; Squire, 1977; Dornbush & Williams, 1974). They are thus considered undesirable and often largely avoidable side effects of ECT.

General Aspects of ECT-Induced Memory Dysfunction

ECT can induce both retrograde and anterograde amnesia and has deleterious, though generally variable and transient, effects on immediate, intermediate, and remote memory (Fink, 1977). It has relatively little effect on short-term memory; its major impact is therefore on long-term memory (Dornbush & Williams, 1974; McGaugh & Williams, 1974).

Bilateral ECT seems to accelerate the process of normal forgetting (Squire, Wetzel, & Slater, 1978). Immediately following each treatment it induces a global anterograde amnesia which by 30 to 45 minutes later has become a well-circumscribed deficit characterized by good immediate memory, rapid forgetting, and temporally graded retrograde amnesia occurring in the absence of confusion or intellectual impairment (Squire et al., 1978; Squire, 1977). After ECT, memory performance is best on recognition testing and worst on recall testing, with relearning intermediate but tending to be more similar to recall than recognition (Dornbush & Williams, 1974). Evaluation of the ability to retain information following ECT is most sensitivity accomplished by the use of recall or relearning rather than recognition testing paradigms. While the ability to recall information is generally more important to patients than simple recognition, it is also considerably more difficult to test.

With ECT there is amnesia (of variable duration) for the seizure itself as well as for immediate pre- and posttreatment periods (Fink, 1977). While memory impairment is typically seen immediately after a treatment is over, its onset may occasionally be delayed for up to 24 hours (Hargreaves, Fischer, Elashoff, & Blacker, 1972). In general terms, Ottosson (1968) has described ECT as transforming the memory disturbance associated with depression from one characterized by poor learning with normal retention to one characterized by normal learning with poor retention.

It is believed that the severity and duration of ECT-induced memory impairments are positively correlated with the number, frequency (Squire & Miller, 1974; Korin et al., 1956; Dornbush, Abrams, & Fink, 1971; Fromholt, Christensen, & Stromgren, 1973), and intensity (Fink, Kahn, & Green, 1958; Ottosson, 1960; McGaugh &

Alpern, 1966) of the electrical stimuli given as well as of the seizures experienced (Laurell, 1970; Ottosson, 1960; Small & Small, 1972).

While increased frequency of treatments may have important implications with bilateral ECT, this may not be the case with unilateral nondominant ECT. Thus, Stromgren, Christensen, and Fromholt (1976) found that four unilateral nondominant treatments per week, as opposed to two, resulted in greater improvement in memory due presumably to more rapid improvement in the underlying depression. Likewise, Abrams (1967) found no greater memory impairment when unilateral nondominant ECT was given on a daily basis as opposed to three times a week.

While early studies suggested that alternating current sine wave stimuli caused more severe cognitive effects than other types of stimulus waveforms (Lieberson, 1953; Valentine, Keddie, & Dunne, 1968), more recent work has indicated that differences between brief pulse and sinusoidal waveform are not likely to be major factors in determining the degree of memory dysfunction associated with ECT (Weaver, Ives, Williams, & Nies, 1977; Weiner, Rogers, Davidson, & Miller, 1981; Spanis & Squire, 1981).

Some work with multiple monitored ECT has reported that it causes both anterograde and retrograde memory disturbances no greater in extent and severity than those seen after a single conventional treatment of the same type and of lesser proportions than if the same number of seizures had been induced individually on an alternate day schedule (Abrams & Fink, 1972).

Giving ECT via unilateral as opposed to standard bilateral administration substantially decreases the extent of memory impairment. Treating unilaterally over the nondominant or dominant hemispheres will also result in major differences in the kinds of memory impairment that occur. These differences will be discussed in detail in a later part of this review.

Administering ECT via anterior bifrontal (Inglis, 1970; Abrams & Taylor, 1973) as opposed to standard bitemporal electrode placement has been reported to lead to a reduction in memory dysfunction while achieving therapeutic efficacy intermediate between unilateral and bilateral ECT.

Stimulating unilaterally over various combinations of anatomic areas seems to have relatively little effect on memory dysfunction. Thus, there is no difference in the impact on memory between nondominant unilateral fronto-parietal and temporo-parietal lead placements (d'Elia & Widepalm, 1974). The findings are somewhat more complex in regard to comparison between fronto-frontal and temporo-parietal lead placements. While two earlier studies reported no difference in anterograde memory function between them both for verbal as well as nonverbal material (d'Elia, 1976; d'Elia, Frederiksen, Raotma, & Widepalm, 1977), a later study reported less retrograde amnesia with fronto-frontal as compared to temporo-parietal stimulation (d'Elia, 1981).

One study has indicated that the degree of immediate memory dysfunction following ECT is highly correlated with the rise in systolic blood pressure that occurs during treatment (Hamilton, Stocker, & Spencer, 1979).

Memory research in animals has shown that material ordinarily not affected by ECT may be forgotten if a reminder of it is presented just before a treatment is given (Schneider & Sherman, 1968; Misanin, Miller, & Lewis, 1968; Lewis, Bregman, & Mahan, 1972). This is known as the "reinstatement phenomenon." The evidence available (Squire, Slater, & Chace, 1976) suggests that this phenomenon does not occur in humans given ECT.

ECT-Induced Anterograde Amnesia

Both bilateral and unilateral ECT can cause anterograde amnesia which is the inability to incorporate material newly learned after ECT into long-term memory storage (Squire & Miller, 1974; Squire et al., 1976; Fleminger, Horne, Nair, & Nott, 1970a; d'Elia, 1974; Halliday, Davison, Browne, & Kreeger, 1968). Adequate investigation of ECT-induced anterograde amnesia requires the use of both immediate and delayed recall assessment devices. This is because tests of delayed reproduction which predominantly reflect retention are generally more sensitive to the deleterious effects of ECT than are tests of immediate reproduction which predominantly reflect new learning ability (Squire & Miller, 1974). Over the course of several treatments new learning ability may actually be improved. Sub-

tracting delayed from immediate reproduction scores yields a highly useful direct measure of memory function, the so-called "forgetting score" (Harper & Wiens, 1975).

The severity of ECT-induced anterograde amnesia depends on the temporal distance from ECT of the new learning. Thus, in a study by Squire et al. (1976), recognition memory for material learned 3 hours after bilateral ECT was significantly better than for that learned 1 hour or less after ECT. Furthermore, the ability to retain material over a short (e.g., 30-minute) period recovers rapidly after ECT, being nearly normal by 3 hours after treatment. There is no cumulative impairment in this short-term measure over the first four treatments. However, the ability to retain new material over longer periods such as 24 hours appears to be much more vulnerable to the effects of ECT. Thus impairment in 24-hour retention was more severe than that seen with short-term retention given comparable amounts of ECT, and the effects of ECT were cumulative. Based on these observations, the theories that ECT causes anterograde amnesia by disrupting the ability to transfer material from short-term memory to long-term memory or to recall material from long-term memory have been advanced.

On the other hand, Squire et al. (1976) postulated that anterograde amnesia results from an ECT-induced impairment of acquisition and consolidation of new information, rather than an impairment of the ability to call upon and use information that has already been stored. Others (Cronholm & Ottosson, 1961, 1963) have suggested that ECT interferes with the memory function, retention, while concomitantly improving new learning, i.e., acquisition and consolidation, to the extent that it reverses the patient's depression. Thus, ECT may have a mixed effect on various aspects of memory function.

ECT-induced anterograde amnesia does not appear to depend on the presence of intellectual dysfunction, confusion, or disorientation following ECT. In general, it gradually recedes after each individual treatment but may be cumulative over a series of treatments (Squire & Miller, 1974).

In 1958, Lancaster, Steinert, and Frost first reported that memory and cognitive impairment due to ECT could be reduced without a major diminution in therapeutic efficacy by using unilateral rather than bilateral stimulation. Subsequently, a variety of studies clearly documented that bilateral ECT produced greater amounts of anterograde amnesia than did either unilateral nondominant (Halliday et al., 1968; Fleminger et al., 1970a; d'Elia, 1970, 1974) or unilateral dominant ECT (Jackson, 1968).

In the mid- to late sixties evidence began to accumulate that there was a differential effect of unilateral dominant and nondominant ECT on verbal and nonverbal visuospatial anterograde memory. This was based on ECT studies that employed assessment batteries which specifically tapped verbal and nonverbal memory function.

Zamora and Kaelbling (1965), using Form One of the Wechsler Memory Scale, found that unilateral dominant ECT caused deterioration in verbal memory performance whereas unilateral nondominant ECT enhanced it, an effect they attributed to ECT-induced improvement in depression in the patients they studied. However, since the instrument they used did not include delayed reproduction subtests, it is more likely that they were measuring differences in new verbal learning ability rather than true verbal memory function.

Subsequently, a study by Jackson (1968) comparing verbal and nonverbal memory effects of right and left unilateral as well as bilateral ECT showed that patients treated with right unilateral ECT had the least verbal memory impairment; those treated with left unilateral, the least nonverbal visuospatial impairment; and those treated with bilateral the greatest degree of both. Similar findings were also reported by Halliday et al. (1968), Cohen, Noblin, Silverman, and Penick (1968); and Zinkin and Birtchnell (1968).
chnell (1968).

Kozma and Galbraith (1968) reported similar results in that they noted improvement in memory with unilateral nondominant ECT, some deterioration with unilateral dominant, and marked deterioration with bilateral ECT.

Sutherland, Oliver, and Knight (1969), in a double-blind study comparing the effects of unilateral dominant, unilateral nondominant, and bilateral ECT on memory function, found that all three types of treatment improved it, and attributed this to the indirect beneficial effect of improvement in depression on cognitive and

memory function. They, like others, found that the greatest degree of improvement occurred with unilateral nondominant ECT.

Two years later Cronin, Bodley, Potts, et al. (1970) showed that impairment of anterograde verbal memory as assessed by word learning and the Wechsler Memory Scale was less marked with unilateral nondominant than with either unilateral dominant or bilateral ECT. Also in 1970, Fleminger, Horne, and Nott, (1970b) reported anterograde verbal memory to be more impaired after left unilateral than right unilateral ECT.

Two more recent well-designed and executed studies (Squire & Slater, 1978; Robertson & Inglis, 1978) have provided further confirmation of the differential effects of various types of ECT on verbal and nonverbal memory. The first study, using a before and after five-treatment design, showed that right unilateral ECT impaired delayed retention of nonverbal material in the form of faces, designs, and spatial relations, without affecting delayed retention of verbal material in the form of a paragraph. In this study, as in earlier ones, bilateral ECT caused greater impairment of both verbal and nonverbal memory than right unilateral ECT. The second study, using more sophisticated dimensions of symbolism and imagery in addition to the usual verbal and nonverbal dimensions in memory testing, further confirmed the differential effects of unilateral nondominant and bilateral ECT on verbal and nonverbal memory function. Unlike earlier studies, neither of these studies directly assessed the effects of unilateral dominant ECT on verbal and nonverbal memory.

Several of the studies that showed clear-cut differential effects of various forms of ECT on memory function reported virtually identical degrees of therapeutic efficacy (Fleminger et al., 1970a; d'Elia, 1974; Halliday et al., 1968; d'Elia & Raotma, 1975). Other studies have disputed the notion that unilateral and bilateral ECT are equipotent (Abrams, Fink, Dornbush, et al., 1972; Abrams, Taylor, Faber, et al., 1981; Price, 1980). Thus, whether or not the risk-benefit ratio (Fink, 1978, 1979) with respect to potential memory effects clearly favors unilateral nondominant over bilateral ECT in all cases is at present unclear and is an issue the APA Task Force on ECT felt should be left up to the clinical judgment of individual practitioners (APA Task Force Report on ECT, 1978).

Relatively few studies have attempted to establish the duration of ECT-induced anterograde amnesia. Halliday et al. (1968) reported that verbal memory impairment persisted over at least a 3-month period after unilateral dominant ECT. This study also indicated that nonverbal memory impairment persists longer after bilateral than unilateral nondominant ECT. Bidder, Strain, and Brunschwig (1970) found verbal memory as assessed by a paired-associate learning test to have returned to baseline within 30 days of the end of courses of both unilateral and bilateral ECT. At the followup assessment, memory was better than it had been before treatment in both groups. Finally, Cronin et al. (1970) showed that differences in anterograde verbal memory resulting from unilateral dominant, unilateral nondominant, or bilateral ECT persisted for 4 to 6 weeks following a course of eight treatments.

ECT-Induced Retrograde Amnesia

As mentioned previously, retrograde amnesia, which is a lack of ability to recall events occurring prior to ECT, also occurs as a result of both bilateral and unilateral ECT though to a significantly lesser extent with the latter (Cohen et al., 1968). It is more severe with increased number and frequency of bilateral ECTs and is thought by some to increase in severity with increasing patient age (Squire, 1974; Fink, 1977), though not all researchers agree on this (Fink, 1979). It often occurs in association with confusion, disorientation, or impairment on the verbal portion of the Wechsler Adult Intelligence Scale (WAIS) (Squire, 1974), but can also be present as an isolated defect.

ECT-induced retrograde amnesia occurs for both public and autobiographical events both temporally close in occurrence to (Harper & Wiens, 1975; Dornbush & Williams, 1974; and Dornbush, 1972), as well as many years (even up to 20) prior to treatment (Squire, 1977; Squire et al., 1975; Squire, 1975; Squire, Chace, and Slater, 1976; Brody, 1944; Squire, 1974; Janis, 1950). In the past the standard explanation for retrograde amnesia due to ECT had been the

"consolidation hypothesis," which held that ECT somehow disrupted neural mechanisms and processes underlying the consolidation of memory traces (Zinkin & Birtchnell, 1968; McGaugh & Williams, 1974). Current theories, however, focus more on ECT-induced interference with the "retrieval process" as the underlying mechanism (Patterson, Lawler, & Rochester, 1978).

There is a temporal gradient in retrograde amnesia induced by ECT (Squire, 1975; Squire, 1976). Thus it was shown that following five bilateral ECTs, television programs broadcasted 1 to 3 years before ECT were forgotten, whereas those broadcasted 4 to 17 years before ECT were not.

Long-term memory for temporal order, which depends on recall not just recognition, appears to be more sensitive to bilateral ECT than other aspects of memory and is, like other forms of retrograde amnesia, associated with a temporal gradient of impairment (Squire et al., 1976). Thus temporal sequencing of events occurring from 4 to 7 years before ECT was impaired, whereas it was not impaired for events 8 to 16 years before. This temporal sequencing impairment persisted unchanged for 1 to 3 weeks after the end of treatment.

d'Elia (1970) reported that unilateral nondominent ECT caused less retrograde amnesia than bilateral ECT with unilateral dominant intermediate between them.

Cohen et al. (1968) showed that five unilateral dominant ECTs selectively impaired retrograde verbal memory, while five unilateral nondominant ECTs selectively impaired retrograde nonverbal, visuospatial memory. They also showed that both verbal and nonverbal memory were more profoundly impaired by five bilateral ECTs than with a comparable number of administrations of either form of unilateral treatment.

Berent, Cohen, and Silverman (1975) replicated the findings of Cohen et al. (1968) after one unilateral nondominant, unilateral dominant, or bilateral ECT, using words or visual forms learned 24-48 hours before and tested 5 hours after ECT. Based on their observation that verbal memory impairment after five unilateral dominant ECTs was much greater than after one, whereas visuospatial memory impairment was nearly identical after both five and one unilateral nondominant treatments, they suggested that the left hemisphere and verbal memory might be more susceptible to the cumulative effects of a series of ECTs than the right hemisphere and visuospatial memory.

Clearing of retrograde amnesia following ECT occurs as a result of spontaneous recovery not via relearning or "prompting" (though this may indeed help). As would be expected from Ribot's Law of Regression (Ribot, 1885), there is greater recovery of more remote events, months to years before ECT, than of very recent events, within days of treatment, for which loss of memory may be permanent (APA Task Force Report on ECT, 1978). Ease of restitution of retrograde memory loss is directly related to the patient's motivation to remember forgotten material, the degree of personal importance and hence presumably the amount of attention paid to it, the amount of affect associated with it, the degree of familiarity with it, and the ease with which it was originally assimilated into memory storage (Williams, 1975).

Recovery from ECT-induced retrograde amnesia occurs over a variable and, thus far, not definitely determined period of time. Various studies have demonstrated persistence of retrograde amnesia over periods ranging from 24 hours (Squire, 1975) to 10 to 14 weeks (Janis, 1950), to as much as 1 year or more following ECT (Brody, 1944). The last was an early study which was uncontrolled, and assessed memory function with respect to familiar, long-known names of persons and places as well as habits of work. Several more recent studies have indicated that the recovery of memory for remote events may be substantially complete in as little as 1 to 2 weeks (Squire, 1975, 1976) or as much as 6 to 9 months post-ECT (Squire & Chace, 1975; APA Task Force Report on ECT, 1978; Squire, 1980; Squire et al., 1980). The latter two studies indicated that memory impairment for events occurring more than 2 years before ECT, as well as new learning capacity, return to normal by 6 months post-ECT. While impaired memory for events occurring during the 1- to 2-year period before ECT substantially improves over the 6 months following ECT, there may be permanent loss of memory for some of them. Most of these permanent memory "gaps" are irritating but not functionally incapacitating to the patient (Freeman, Weeks, & Kendell, 1980).

Followup Studies of Long-Term Effects of ECT on Memory

Assessing the long-term effects of ECT on memory function is difficult because, as was first described nearly 20 years ago (Cronholm & Ottosson, 1963), and more recently confirmed (Squire & Chace, 1975), patients' subjective experience of their memory function is often at odds with the results of objective testing. In general, a patient's subjective assessment of the adequacy of his or her memory function post-ECT is directly related to verbal but not visuospatial performance, the degree of affective improvement from ECT, and the adequacy of immediate reproduction capacity, i.e., learning, more than delayed reproduction capacity, i.e., retention (Cronholm & Ottosson, 1963). Given the numerous and potentially complex interactions that may occur between these variables, it is not surprising that subjective and objective assessments of memory are often at variance with each other.

Squire and Chace (1975) found no objective difference in new learning, retention memory scores, remote memory, or self-rating of memory function 6 to 9 months after unilateral nondominant or bilateral ECT or inpatient psychiatric treatment without ECT. Despite the lack of objective differences, 63% of prior bilateral ECT patients felt their memory was not as good as it had been before treatment, while only 30% of unilateral ECT patients and 17% of non-ECT-treated patients felt similarly.

Squire et al. (1979), using a self-report memory assessment scale, found that subjective complaints of memory impairment persist in a gradually diminishing fashion for up to 6 months after ECT. The complaints present 6 months after ECT differ qualitatively from the depression-associated complaints present prior to ECT and are similar to, but less marked than, those present 1 week following ECT. Thus, while their etiology is unclear, the authors suggested that they are unlikely to be due to such commonly advanced explanations as persistent low self-esteem, a general tendency to complain about memory capacity, or recurrent depression-associated memory dysfunction.

Freeman, Weeks, and Kendel, (1980) retrospectively studied patients who had had ECT (mainly bilateral) from 2.6 to 12.8 years (mean = 10 years) previously and who complained of permanent unwanted effects secondary to the ECT. They found these patients to be more depressed and anxious and to be taking more psychotropic medications than the noncomplainers. Nonetheless, even after partialling out the effects of these factors, they still found more impairment in the patients than in volunteer, nonpatient controls on 3 out of 19 wide-ranging cognitive and memory tests. In fact, a few of the patients scored in the organically-impaired range on some of the tests. The authors concluded that: ECT may induce permanent memory impairment in a very small proportion of patients who receive it; this memory loss is, for the most part, irritating but not incapacitating; and that ECT does not normally produce persistent memory defects in most patients.

In a related study, Weeks, Freeman, and Kendell (1980) studied unilateral nondominant and bilateral ECT patients as well as normal and non-ECT-treated patient controls with a battery of tests that assessed both memory and non-memory associated cognitive function. These tests assessed recall, relearning, and recognition functions in auditory, verbal, and visuospatial modes. They also tested immediate and delayed retrieval, short and long-term memory, as well as remote (long-term) memory for both personal and impersonal material. They found that unilateral nondominant ECT patients scored close to normal controls on many of the tests after 1 week of treatment; whereas, bilateral ECT patients showed significantly greater impairment after 1 week. At 3-month followup, however, unilateral nondominant and bilateral ECT patient performances were identical. At 4- and 7-month followups both ECT patients and non-ECT patient controls showed deficits on some tests when compared to the normal controls. They also complained subjectively of memory deficits which were attributed to the effects of residual depression, medication, and/or persistent ECT-induced memory impairment.

While there have been several anecdotal reports of patients who have received very large numbers of ECT with no apparent cognitive or memory impairment, such as that of Perlson's (1945) male patient who had received 248 bilateral ECTs, other reports (Templer, Ruff, & Armstrong, 1973; Goldman, Gomer, & Templer, 1972; Teuber, Corkin, & Twitchell, submitted) have raised the possibility

that large numbers of bilateral ECT (more than 50 treatments per patient) may be associated with impairment on a variety of memory tests not present in controls on followup testing many years later. The conclusion of these studies that ECT is responsible for the observed persistent impairment must be viewed with caution since, given their design and retrospective nature, the effects of underlying chronic schizophrenia, depression, and/or associated organic lesions such as cingulotomy cannot be separated from the effects of ECT.

Summary

From this review a variety of reasonably firm conclusions about the effects of ECT on memory can be drawn. These include:

1. ECT causes both retrograde and anterograde amnesia.
2. Bilateral ECT causes greater anterograde amnesia than unilateral nondominant or dominant ECT, both for nonverbal and verbal memory.
3. Anterograde amnesia severity depends on the temporal distance from ECT of the new learning in question.
4. Anterograde amnesia recedes gradually after each individual treatment, but is cumulative over a series of treatments.
5. The early time course of recovery of anterograde amnesia due to ECT is not clear but is substantially complete by at least 6-9 months post-ECT.
6. Bilateral ECT causes greater retrograde amnesia than unilateral dominant and nondominant ECT, both for verbal and nonverbal memory.
7. Retrograde amnesia is characterized by a temporal gradient, and recall of when events occurred intime is more sensitive to impairment than other aspects of retrograde memory.
8. Unilateral nondominant ECT selectively impairs nonverbal retrograde memory, while unilateral dominant ECT selectively impairs verbal retrograde memory.
9. Recovery from retrograde amnesia following ECT is substantially complete by 6-9 months; however, some events during the 1-2 years before ECT and events during the course of treatment may be lost permanently.
10. ECT-induced memory dysfunction appears to be qualitatively different than depression-related memory dysfunction, at least as assessed by self-report scales.
11. Despite lack of objective evidence of memory dysfunction several months post-ECT, patients will often complain of subjective memory impairment following treatment. These complaints are more frequent following bilateral than unilateral ECT.
12. ECT, in a small number of patients, may cause permanent memory impairment; the functional significance of this memory loss is unclear at present.
13. ECT does not normally cause enduring memory deficits, and with unilateral nondominant ECT there is generally relatively little clinically apparent memory disturbance even immediately following ECT.

Areas for Future Research

Despite the extensive investigation of the effects of ECT on memory function over the past two decades and despite the fact that, as this review indicates, much is known about this area with a reasonable degree of certainty, many questions remain, and these indicate important directions for future research.

For example, what is the true incidence of permanent memory dysfunction from bilateral ECT? Does it ever occur in patients treated with unilateral ECT? If so, how often, and is the type of dysfunction different than that seen with bilateral ECT? Is it possible to identify, prior to treatment, through biological markers or clinical profiles, that small but finite number of patients who will be prone to experience permanent ECT-induced memory impairment? Can the nature and functional significance of such deficits be better characterized, especially with respect to the kinds of impact they have on the patient's life and work?

How long do subjective memory deficits persist post-ECT and what relationship do they bear to permanent memory impairments on objective memory tests?

How do ECT, particularly unilateral nondominant ECT, and various commonly used drug treatments for depression compare in regard to causing cognitive or memory disturbances in the short-run, but even more importantly over extended followup periods after acute treatment?

Does ECT have differential effects on memory function in different diagnostic groups, for example, in patients with schizophrenia as opposed to patients with major depressive disorders? Some early studies suggested that there might be such differences but this issue has not been adequately examined with studies using rigorous experimental designs in patient populations carefully defined by current research diagnostic criteria.

Studies of the latter type, as well as rigorously designed, prospective controlled studies with long-term followups involving large enough numbers of patients so that solid statistical inferences, regarding observed differences can be drawn, are badly needed. Multicenter, collaborative studies, despite their obvious drawbacks, lend themselves uniquely well to the need to collect large numbers of experimental subjects. Carefully done, large-scale, longitudinal, studies of the incidence, nature, and natural history of various types of ECT-induced memory dysfunction are also sorely needed. Additional rigorously designed and executed studies of the relationship between ECT-induced memory changes and the electrical characteristics (waveform, intensity, duration, frequency, etc.) of the stimulus; the number, frequency, and duration of induced seizures; and various ECT-induced neurophysiological and neuroendocrinological changes would also be important additions to the literature.

Research aimed at developing means of further attenuating, or even preventing altogether, ECT-induced memory loss via additional technical modifications of ECT or pharmacological interventions with, for example, peptide hormone fragments, should also have a high priority. Efforts aimed at identifying the basic mechanisms underlying ECT's therapeutic effects should be encouraged, as these may make it possible to develop an alternate form of treatment that will have comparable therapeutic efficacy without memory impairment.

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Short- and Long-Term Cognitive Effects of ECT: Part II—Effects On Nonmemory Associated Cognitive Functions.

Trevor R.P. Price, M.D.[1]

In addition to the multiple effects that electroconvulsive therapy (ECT) has on memory function, which were reviewed in the preceding article (Price, 1982), it likewise has a variety of effects on cognitive functions which are largely independent of memory. The range of cognitive domains affected include, for example, perceptual function, psychomotor speed, visuomotor ability, simple and complex sensory capacity, complex discrimination ability, and synthesizing and abstracting ability (Fink, 1979). This article will review these effects of ECT.

To understand ECT's effects on memory function or nonmemory-associated cognitive and neuropsychological function, it is important to

[1]Department of Psychiatry, Dartmouth Medical School, Hanover, NH 03755.

keep in mind that the diseases for which ECT finds its principal use, i.e., major depressive disorder and schizophrenia, may themselves be responsible for significant deviations from the norm in these functions. Thus the problem of how much of an observed cognitive impairment is due to the treatment as opposed to the underlying disease again confronts the clinician. For a more detailed discussion of this issue, the reader is referred to the discussion by Nasrallah in this series.

Nonmemory Cognitive Impairments Associated with Depression

Depression may be associated with nonmemory-associated cognitive dysfunctions, ranging from impaired concentration and attention (Wohlberg & Kornetsky, 1973) to a state-dependent delirium with mild to moderate, diffuse, generalized impairment on the Halstead-Reitan battery (Donnelly, Dent, & Murphy, 1972; Goldstein, Filskov, Weaver, & Ives, 1977) to the clinical picture of a profound pseudodementia with gross cognitive impairment and marked general function disability (Wells, 1979; Cavenar, Maltbie, & Austin, 1979). Unfortunately, the research literature in this area is inconsistent and at times even somewhat contradictory. For example, Small, Small, Milstein, and Moore (1972) reported no evidence of diffuse of localized neuropsychological dysfunction on Halstead-Reitan testing in a cohort of psychotically depressed patients but, subsequently, in a followup study of the same patients, reported improvement in some right hemispheric functions with ECT, suggesting the likely presence of an unrecognized asymmetric abnormality prior to treatment (Small, Small, Milstein, & Sharpley, 1973). Several other workers have also reported right hemispheric, particularly frontal, abnormalities (Tucker, Stenslie, Roth, & Shearer, 1981; Kronfol, Hamsher, Digre, & Waziri, 1978; Goldstein et al., 1977), as well as atypical patterns of hemispheric activation (Moscovitch, Strauss, & Olds, 1981) and impaired ability to learn new material (Campbell, 1957), to note just a few of the many different types of cognitive dysfunction that may be associated with depression.

Despite these interesting and provocative preliminary findings, thus far no characteristic patterns of cerebral dysfunction of hemispheric asymmetry occurring in association with depression have been clearly established (Marin & Tucker, 1981).

Cognitive Impairment Associated with Schizophrenia

In patients with schizophrenia, a variety of nonmemory-associated cognitive impairments have been found. As with depression, impaired attention and concentrating ability are common (Wohlberg & Kornetsky, 1973), as is diffuse cognitive dysfunction as assessed by the Halstead-Reitan battery as well as other tests of neuropsychological function (DeWolfe, Barrell, Becker, & Spaner, 1971; Watson, 1971). Wexler (1980) described specific left hemispheric dysfunction in schizophrenia in his review of the literature on cerebral laterality and psychiatric illness. Others (Taylor, Greenspan, & Abrams, 1979; Newlin, Carpenter, & Golden, 1981) have reported similar findings. However, Marin and Tucker (1981) and Merrin (1981) note that while some studies seem to support the notion of specific left hemispheric dysfunctions in schizophrenia, a variety of others do not. They also point out the existence of a variety of methodologic shortcomings in many of the studies that have been done in this area.

Methodological and Technical Issues

In view of the foregoing, it is clear that any research on the nonmemory-associated cognitive effects of ECT must be designed and executed so as to carefully control for and, as much as possible, eliminate the following confounding factors.

First, one must anticipate finding impaired attention and concentration as well as diffuse cognitive dysfunction in both depressives and schizophrenics. Next, presumed lateralized ECT-induced cognitive changes must be interpreted in the light of the evidence that suggests there may be differential right hemispheric dysfunction in depression and left hemispheric dysfunction in schizophrenia. One must attempt to control for patient age, treatment with psychotropic medication, intelligence quotient (IQ), education, and severity of illness, given the potentially important

impact each of these may have on various cognitive functions. It is thus important that studies of the effects of ECT on cognition include age- and IQ-matched, comparably ill, medication-free, patient controls as well as normal controls.

It is also crucial to design cognitive test batteries with the practice effect in mind. Finally, in this type of research it is important to determine accurately hemispheric dominance, since just giving right unilateral ECT to all patients can result in stimulation over the dominant hemisphere in as many as 10% of cases even among strong right-handers (Clyma, 1975). Testing for dysphasia after ECT (Warrington & Pratt, 1973; Pratt & Warrington, 1972) and using the handwriting test (Levy & Reid, 1976), in addition to administering standard handedness questionnaires, can significantly increase the accuracy of determining cerebral dominance.

General Principals Regarding the Effects of ECT on Nonmemory-Associated Cognitive Function

In general, the literature during the 1940s and 1950s on nonmemory-associated cognitive effects of ECT was somewhat more extensive than that regarding the effects of ECT on memory. However, interest in this area waned in the 1960s and 1970s, though in very recent years there appears to have been a resurgence of research interest in this area in conjunction with the growth of interest in topics such as the laterality of cerebral functions, the neuropsychological abnormalities associated with various types of psychopathology, and the differential effects of dominant and nondominant unilateral ECT.

Fink (1979) reported that ECT-induced impairments in certain neuropsychological functions, e.g., perceptual acuity and psychomotor speed, are proportional to the number and frequency of seizures induced. As is the case with memory dysfunction, ECT-induced cognitive dysfunction may be delayed in its onset for up to 24 hours (Hargreaves, Fischer, Elashoff, & Blacker, 1972). Further, it has been reported that the impairments in nonmemory-associated cognitive functions are maximal at the time of the seizure and rapidly revert to pretreatment levels or better during the 14 days following the last seizure. Some evidence suggests that there is a cumulative effect on certain cognitive measures, such as the verbal Wechsler Adult Intelligence Scale (WAIS). Thus, Squire (1975) reported that the verbal WAIS had returned to normal within 40 minutes of the first bilateral ECT in a series, but took up to 48 hours to return to normal after the sixth. Three other studies suggested that with unilateral ECT, performance on a variety of psychological tests deteriorates progressively up to the fifth treatment, then improves despite continued treatment (Small & Small, 1971; Scanlon & Mathas, 1967; Fink, Kahn, Kapp, et al., 1961). Not surprisingly, simple cognitive and neuropsychological functions tend to be less severely disrupted and to return to baseline more rapidly than do complex ones.

In addition to the general changes in neuropsychological function already mentioned, ECT can cause topographical disorganization and disorientation (A Practicing Psychiatrist, 1965). Another interesting but as yet unexplained finding is that the number of errors on the Benton Visual Retention Test correlates highly with the degree of rise in blood pressure that occurs during ECT (Hamilton, Stocker, & Spencer, 1979). Furthermore, analogous to its effects on memory, unilateral dominant ECT has been reported to have greater effects on verbalization than is the case with unilateral nondominant ECT (Pratt & Warrington, 1972). Curiously, patients who have had unilateral dominant or bilateral ECT have been found to have greater difficulty with picture recognition than those who received unilateral nondominant ECT (Halliday, Davison, Browne, & Kreeger, 1968). This is thought to be due to the important influence verbal functions play in encoding visual stimuli (Williams, 1973), a role perhaps even more important than that of visual perceptual factors.

Unlike memory functions, there has been a relative paucity of investigation of the relationship between nonmemory-associated cognitive functions and stimulus intensity and waveform, the location (laterality) of stimulation, and the interaction between the cognitive effects of ECT and patient age, IQ, and sex. In fact, it has only very recently become apparent that the last-mentioned of these variables may be important in relation to general cognitive functioning (Miller, Small, Milstein, et al., 1981; Inglis & Lawson, 1981).

The Clinical Spectrum of ECT-Induced Nonmemory-Associated Cognitive Dysfunctions

Post-ECT cognitive dysfunctions span a broad spectrum of clinical presentations ranging from no apparent dysfunction to mild delirium with confusion all the way to gross delirium with flagrant organic psychotic features.

Post-ECT Confusion

Since post-ECT confusion is so frequently seen, it has, not surprisingly, been studied by a number of researchers over the years. Unfortunately, many of the articles dealing with it have failed to provide adequate operational definitions of "confusion" and have not established objective criteria for quantitative measurement of it. Despite these shortcomings, there seems to be a general consensus in these studies that bilateral ECT causes a greater degree of confusion and confusional behavior than unilateral ECT (Lancaster, Steinert, & Frost, 1958; Cannicott, 1962; Impastato & Karliner, 1966). Impastato and Karliner (1966) further reported that the degree of confusion occurring after unilateral nondominant ECT was less than that observed after unilateral dominant ECT. Consistent with this finding was that of Abrams (1967), who reported that neither confusion nor confusional behavior occurred after unilateral nondominant ECT, even when it was given on a daily basis for a large number of treatments.

Some researchers seeking to quantify the somewhat nebulous notion of confusion have employed as an objective measure the amount of time necessary after ECT for patients to regain full orientation to person, place, and time. Using this operational definition, several workers including Valentine, Keddie, and Dunne (1968); Halliday et al. (1968); Sutherland, Oliver, and Knight (1969); and d'Elia (1970) have replicated and confirmed the qualitative findings of earlier studies that unilateral ECT is followed by more rapid reorientation, and therefore less confusion, than is bilateral ECT. Fraser and Glass (1978, 1980) using a quantitative index of recovery after ECT that included, among other measures, orientation time, found that recovery was more rapid after unilateral nondominant than after bilateral ECT. Furthermore, they found that the recovery time after bilateral but not unilateral nondominant ECT increased as the course of treatment progressed, especially if the interval between treatments was shorter, e.g., 1 day, as opposed to 2 or 3 days. They also found that recovery times were longer in elderly as opposed to young patients with both unilateral and bilateral treatment modes. The differences were five times greater with unilateral and nine times greater with bilateral ECT.

Several other related studies have confirmed the fact that reorientation occurs considerably more rapidly after unilateral nondominant than unilateral dominant or bilateral ECT (Halliday et al., 1968; Sutherland et al., 1969; Wilson & Gottlieb, 1967; Cronin, Bodley, Mather, et al., 1970; d'Elia, 1970).

As is true with memory dysfunction following ECT, post-ECT confusion does not have prognostic implications as far as treatment outcome is concerned, nor is it a necessary concomitant of affective improvement. Thus, Wilcox (1953) found that there was no relationship between prolonged confusion after the first ECT, nor the degree of cumulative confusion after the tenth ECT in a series, and the results of a full course of ECT, either in respect to affective or cognitive outcome.

Acute Organic Mental Syndromes

ECT-induced acute organic mental syndrome, as it is currently known, is a clinical syndrome characterized by variable symptomatology ranging from mild confusion and bewilderment to grossly psychotic signs and symptoms in association with global cognitive impairment. It was first described in 1945 by Kalinowsky and has since been reported in a number of studies (Gallinek, 1952; Ottosson, 1968; Elmore & Sugerman, 1975; Arnot, 1975; Summers, Robins, & Reich, 1979; Fink, 1979; Marshall, Kalin, & Tariot, 1980).

This syndrome may be characterized by any or all of the following: difficulty concentrating, gross disorientation and confusion, a sense of perplexity and bewilderment, perseveration and circumstantiality, aphasic and apraxic symptoms, facial and body dysgnosias, and hallucinations and delusions (Kalinowsky, 1945). Typically such

episodes clear suddenly and, according to Kalinowsky (1945), they frequently clear within 7 to 10 days of their onset.

In a recent series (Summers et al., 1979), 40% of patients receiving bilateral ECT developed acute organic mental syndromes. These varied in severity, developed after a mean of 5.5 bilateral ECTs, had a mean duration of 20.1 days, and were seen more frequently in patients with a history of major medical illness or in patients who were on psychotropic drugs, especially drugs having anticholinergic effects. The last finding, of course, is consistent with the widespread clinical experience that ECT and anticholinergic agents may have additive deliriogenic effects. Similarly, a number of recent reports (Ayd, 1981; Mandel, Madsen, Miller, & Baldessarini, 1980; Small, Kellams, Milstein, & Small, 1980; Weiner, Whanger, Erwin, & Wilson, 1980) indicate that ECT and lithium in combination may have a particular propensity in some, but not all, patients to cause reversible acute organic mental dysfunction.

Fink (1974) has reported an increased frequency of acute organic mental syndromes with increased numbers and frequency of bilateral ECTs. Abrams and Fink (1972) also reported, in a preliminary fashion, that the incidence of prolonged organic confusional states seemed to be greater with multiple monitored than with comparable conventional ECT.

A variety of other related post-ECT phenomena have also been reported. Gottlieb and Wilson (1965) reported dysphasia in the form of mumbling and jargon speech especially after unilateral dominant ECT. Clyma (1975) reported finding similar dysphasis in his patients which typically resolved within 30 minutes of ECT. Annett, Hudson, and Turner (1974) also reported that dysphasia, as reflected in a naming task, was more pronounced after left than right unilateral ECT. In this same study, however, no difference between the modes of stimulation could be found in their effects on visual discrimination tasks.

There have been reports of transient neurological signs and symptoms occurring immediately after ECT (Kane, 1963; Kriss, Blumhardt, Halliday, & Pratt, 1978; Impastato & Karliner, 1966). These neurological findings have been mainly contralateral to the side of stimulation, transient with resolution within 20 minutes of treatment, and include decreased contralateral sensory discrimination, transient flaccid hemiparesis and even paralysis, asymmetric deep tendon reflexes, tactile and visual inattention (agnosognosia), and homonymous hemianopsia.

Early Psychometric Studies of Nonmemory-Associated Cognitive Effects of ECT

In the 1940s, in response to fears as to the potential for ECT to cause significant and perhaps even permanent brain damage, Perlson (1945) published a report of a male patient who had received 248 bilateral ECTs over a 2-year time span. When assessed with an extensive battery of tests following this 2-year period, he was found by the author to be of superior ability in comparison to the general population, to have "intellectual ability slightly better than expected for college level performance," and to have experienced no greater change in intellectual functioning than would have normally occurred as a consequence of 2 years of aging.

Stone (1947) reported generalized cognitive dysfunction, of which amnesia was only a part, occurring in association with from 4 to 20 ECTs. He noted that it progressively increased in severity with ECT from prior to the first treatment to from 24 to 30 hours after the last ECT and subsequently gradually diminished over the next 2 weeks. The kinds of post-ECT cognitive impairment he found included: decreased calculating ability, decreased auditory and reading comprehension, decreased ability to think abstractly and perceive interrelationships, decreased ability to make choices and clarify issues, and diminished ability to arrange words or objects according to a specified plan.

Luborsky (1948) found the effects of ECT on cognitive function to differ in schizophrenics and depressives. He gave each patient group a diverse battery of psychometric tests before ECT, after the 10th or 11th treatment, and 5 or 6 days after a completed series of 12 treatments. In the schizophrenics, he found impaired organizational-synthetic, visuomotor, and fluency of association functions after the 10th or 11th treatment in comparison to baseline, which he felt suggested the presence of organic brain dysfunction, but he could find little or no evidence of impair-

ment 5 to 6 days after the last ECT. His depressed patients showed a different pattern, with progressive improvement from baseline to posttreatment testing, without the initial impairment.

Huston and Strother (1948) administered the Babcock and Shipley-Hartford test batteries to depressed patients prior to ECT and 11 days and 6 months after the last treatment. The former battery includes 31 items that assess memory, attention, and psychomotor speed; the latter taps vocabulary and abstract thinking. At 11 days post-ECT, the results on the Babcock were slightly improved. At the 6-month posttreatment followup, statistically significant improvement had occurred with both.

Fisher (1949) demonstrated improvement in a variety of cognitive functions in depressed patients who had improved clinically with bilateral ECT, when pretreatment performance was compared with performance 14 days after treatment. He found significant changes in synthesizing ability, abstracting ability, speed of ideation, visuomotor ability, and estimation of self-performance.

Stone (1950) reported two patients who had received 14 and 20 ECTs, respectively, who manifested neither objective nor subjective diminution in performance on a battery of cognitive and intelligence tests from before to after ECT.

Pascal and Zeaman (1951) reported four patients in whom serial testing was done before, during, and after ECT with four different cognitive tests. These tests were: a noun-naming test, a color-naming test, the Bender-Gestalt, and a serial subtraction test. They found improvement in the tests early in the course of ECT followed by worsening as the course of treatment progressed with return to pretreatment baseline levels or better within several days of the last treatment.

Although their findings appear to be somewhat at variance with other reports in the the literature, Shapiro, Campbell, Harris, and Dewsberry (1958) reported that ECT did not cause an increase and, in fact, probably caused a relative decrease in psychomotor speed. Nor did it reduce the so-called "distraction effect" in which depressed patients doing a paper and pencil maze task speed up their performance when asked to count aloud at the same time.

More Recent Psychometric Studies of Nonmemory-Associated Cognitive Effects of ECT

McAndrew, Berkley, and Matthews (1967), on the basis of a battery of neuropsychological tests sensitive to specific right and left lateralized hemispheric functions as well as some sensitive to diffuse organic impairment without lateralization, given before and after six right or left unilateral or bilateral ECTs, found no statistically significant differences between or within groups. They did find an interesting trend for right unilateral ECT to lead to more frequent improvement on right than left hemisphere tests, for left unilateral to do just the reverse, and for bilateral to lead to identical percentages of improvement on both right and left hemisphere tests. The Halstead categories test, which is sensitive to diffuse cerebral dysfunction, showed identical percentages of improvement (75%) and worsening (25%) among the three treatment groups. In all three groups, after the sixth treatment there was evidence of some transient cerebral dysfunction. These findings suggest that, on the whole, ECT improves nonmemory cognitive function, though it may in some cases and at certain points in the treatment course induce variable degrees of transient diffuse cerebral dysfunction.

Small et al. (1972) tested ECT patients who had been randomly assigned to unilateral nondominant or unilateral dominant ECT with a battery of neuropsychological tests, modified from the Halstead-Reitan and Wechsler test batteries, before ECT, after five treatments, and 60 to 90 days after the last treatment. They found that after five unilateral nondominant treatments several Halstead-Reitan subtests (mainly right-sided) were improved. Five unilateral dominant ECTs did not result in Halstead-Reitan subtest improvement but did result in impaired Story Memory A performance. At followup 60 to 90 days later, the unilateral nondominant group showed sustained improvement, while the unilateral dominant group now had comparable improvement with clearing of the impairment in Story Memory A.

In a related study (Small et al., 1973), it was found that unilateral dominant, unilateral nondominant, and bilateral ECT were all associated with improvement in nonverbal, visuospatial,

nonmemory-related performance tasks and with temporary deterioration on tests requiring intact verbal function. Halstead-Reitan subtests that did change in this study were predominantly in the direction of improvement and were equally distributed among test items reflecting dominant, nondominant, and bilateral hemispheric function.

Reichert, Benjamin, Neufeldt, and Marjerrison (1976) reported that bilateral but not unilateral nondominant ECT produced impairments in "prograde effects" as reflected by decreased performance on the Quick Test, a test of general verbal cognitive processes and performance. These "prograde effects" included motivational, attentional, perceptual, and performance dimensions and therefore play an important role in facilitating information acquisition and storage, but not in mediating recall functions.

Kronfol et al. (1978) studied 18 depressed patients before and during ECT with a battery of neuropsychological tests capable of differentially assessing verbal and nonverbal cognitive functions. Prior to ECT, they found that 5 of the verbal and 13 of the nonverbal subtests were within the impaired range, and interpreted these findings as indicating that depression interferes with both verbal and nonverbal cognitive function but more so with respect to the latter. The posttreatment cognitive testing results, though actually involving relatively small and, for the most part, not statistically significant changes, was interpreted by the authors as indicating that left hemisphere functions declined following left-sided ECT while right hemispheric functions tended to improve after right-sided ECT. They noted disruption of both verbal and nonverbal cognitive tests after one unilateral dominant or nondominant ECT with the degree of verbal impairment being more significant. They interpreted the results obtained after the eighth ECT as reflecting the interaction of two factors, the disruptive effect of ECT in conjunction with the enhancing effect of relief from depression on cognitive processes. Their general conclusion was that ECT did not impair brain functioning but rather brought about significant improvement in nonmemory-related cognitive function as well as in depression.

Consistent with this is the finding of Miller et al. (1981) that the Halstead-Reitan impairment index and verbal, performance, and full-scale IQ scores obtained 2 weeks after a course of ECT are improved when they are compared to those obtained beforehand. As might be expected, the degree of improvement was greater with unilateral than bilateral ECT.

MacKenzie, Price, Tucker, and Culver (1982) compared the daily performance of patients receiving bilateral sinusoidal ECT with that of psychiatric inpatient controls not treated with ECT on a battery of four neuropsychological tests over the first 8 to 12 days of a course of bilateral ECT during which time a mean of 3.1 ECTs had been administered. Both groups improved on all the tests given, but the rate of improvement in the ECT patients was significantly less after three treatments had been given than that in the controls for the Letter Cancellation Test, though not for the others. On the basis of their findings, the authors suggested that some of the earliest effects of bifrontotemporal ECT may be impairment in attentional processes and the capacity to make appropriate shifts in behavioral set, functions thought to be mediated primarily by the frontal lobes (Mattes, 1980; Silverstein, Morrison, & Weinberg, 1980).

Goldstein et al. (1977) found on Halstead-Reitan testing in a small group of psychotically depressed patients evidence of diffuse, generalized, as well as localized right hemispheric dysfunction which was more prominent in patients with a prior history of ECT. There was neither systematic improvment nor worsening in the Halstead-Reitan battery after a course of either brief-pulse or sinusoidal ECT (it is unclear from the study whether the ECT was unilateral or bilateral). However, evidence of right hemisphere dysfunction had increased immediately after treatment and was even more pronounced at 3-month followup. The evidence of generalized, diffuse dysfunction was still present but decreased at 3 months post-ECT. A somewhat similar study done previously by Kendall, Mills, and Thale (1956) had also found no difference between pulse and sine wave stimulation in their effects on cognitive functions.

Horan, Ashton, and Minto (1980) studied depressed patients after three right unilateral ECTs with a battery of tests which tapped four general areas of cerebral functioning including verbal, memory, visuospatial, and visuomotor. The main findings were that the Knox Cube Im-

itation Test performance was improved, whereas other tests in the battery were not. The authors interpreted this finding as suggesting that the left hemisphere is specialized for processing sequential, time-dependent information. Further, they pointed out that unilateral ECT may be a powerful tool for investigating differential hemisphere functioning in cognitive areas other than memory, a research area that has been relatively little explored thus far.

Short- and Long-Term Followup Studies of the Effect of ECT on Nonmemory-Associated Cognitive Function

While relatively few studies have examined the long-term natural history of ECT-induced cognitive dysfunction, a variety of studies, some of which have been previously discussed, have examined the evolution of cognitive dysfunction over relatively short periods of time, i.e., 2 to 3 weeks at most, following ECT. The following are a few selected longer-term followup studies.

Goldman, Gomer, and Templer (1972) compared the results of Bender-Gestalt and Benton tests in 20 male schizophrenics who had received more than 50 ECT (50-219 with a median of 69.5) between 10 and 15 years previously, with matched schizophrenic controls without a history of ECT. They found a higher error rate in the ECT-treated patients and interpreted this as indicating organicity or permanent brain damage secondary to ECT. In view of the lack of control for severity of illness and the use of uncertain diagnostic criteria in this study, this conclusion must be viewed with caution.

Templer, Ruff, and Armstrong (1973) replicated the preceding study controlling for degree of psychosis and found that schizophrenics who had received more than 50 (median 58.5) ECTs at least 7 years before did not differ in WAIS and Benton scores but did have lower Bender-Gestalt scores than schizophrenic controls without a history of treatment with ECT. They interpreted their finding as being consistent with permanent brain dysfunction due to ECT.

Weeks, Freeman, and Kendell (1980) compared the results of a battery of 19 different memory and nonmemory tests administered to depressed patients before, 1 week, 4 months, and 7 months after unilateral nondominant or bilateral ECT to results obtained from non-ECT patient controls as well as normal controls. At 1 week posttreatment, ECT-treated patients did not perform worse on any of the cognitive tests and, in fact, improved significantly on several of them. At 4-month followup, the scores on cognitive tests in the ECT and non-ECT patient groups were virtually identical. At 7-month followup, the same was true except that there was a tendency for both patient groups to have slightly more impaired scores than the normal control groups. When the unilateral and bilateral ECT patients were compared, it was found that the former were significantly less impaired on cognitive testing than the latter at 1 week post-ECT and, in fact, were scoring close to the normal controls on many of the tests. However, at 4 months post-ECT there was no difference between the two ECT groups. The authors conclude that, in general, ECT does not cause lasting cognitive impairment and that with unilateral nondominant ECT there is very little impairment even in the short-term.

Freeman, Weeks, and Kendell (1980) reported that patients who had had ECT in the past, a mean of 10 years previously, and who still complained of cognitive dysfunction secondary to ECT, performed for the most part as well as normal controls on a variety of nonmemory cognitive tests. On the basis of these results, the authors concluded that ECT usually does not produce enduring ill effects on nonmemory-dependent cognitive function.

Summary

Based on this review, several conclusions emerge.

1. ECT causes immediate posttreatment confusion, which may be cumulative over a course of treatment; this posttreatment confusion is considerably less severe with unilateral than with bilateral treatment.
2. ECT does not cause lasting or permanent dysfunction in nonmemory-associated cognitive functions; though there may be initially or at some other point during the course of treatment, transient, reversible evidence of impairment.
3. If such transient impairments do occur, most studies suggest they will have cleared completely by between 2 and 8

weeks after the treatment course is completed.

4. A few studies raise the question of whether or not bilateral ECT may cause some long-lasting cognitive impairments in schizophrenic patients.
5. Overall, ECT improves nonmemory-associated cognitive functions compared to pretreatment baseline scores.
6. In general, effective treatment with ECT seems to improve nonmemory-associated cognitive dysfunctions associated with depression.
7. Unilateral nondominant ECT appears to improve specific right-sided neuropsychological dysfunction associated with depression, whereas unilateral dominant ECT may impair some left-sided neuropsychological funtion.
8. Acute organic mental syndromes are known to occur in up to 40-50% of patients receiving bilateral ECT; whether or not, and how frequently these may occur with unilateral nondominant treatment is not clear.
9. Certain drugs such as lithium and highly anticholinergic psychotropes such as amitriptyline or benztropine may, when given concurrently with ECT, increase the incidence of acute organic mental syndromes associated with it.

Questions for Future Research

Since the whole area of the effects of ECT on nonmemory-associated cognitive function is virtually in its infancy, a broad array of important research questions for the future exists. For example, will the fascinating early findings in regard to specific lateralized cognitive effects of right and left unilateral ECT hold up in future, well-controlled, prospective replicative studies? In this vein, will ECT turn out, as some suspect it may, to be a useful research tool in investigating the lateralization of cerebral hemispheric functions?

Could careful investigation of the relationship between stimulus and seizure variables and ECT-induced cognitive impairment allow for the development of treatment protocols which in terms of stimulus parameters and treatment schedules could optimize treatment efficacy while further minimizing the occurrence, however transient, of cognitive disturbances? Specifically, if, as seems possible, changes in attentional function are among the earliest to occur after bilateral ECT and if, as also seems possible, they occur early on a continuum with more diffuse and flagrant later organic mental symptoms, might it be possible by monitoring them to identify patients at high risk of developing acute organic mental syndrome and, on the basis of these findings, appropriately adjust the number, type, and/or frequency of treatments given.

Will careful future investigation of the beneficial effects of ECT on certain specific cognitive dysfunctions in depression perhaps shed further light on their etiology or perhaps on the basis for some of the therapeutic effects of ECT?

Other important questions include the following. How frequently do acute organic mental syndromes occur after unilateral nondominant ECT and how might their clinical manifestations differ from those that occur after bilateral ECT? If interference with frontal lobe attentional mechanisms is the basis for at least some portion of the post-ECT acute organic mental syndrome, might there perhaps be some pharmacological means of preventing this, such as with Ritalin or Pemoline?

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Nonmemory Higher Cognitive Function and Electroconvulsive Treatment

Sheri A. Berenbaum, Ph.D.,[1] and Michael Alan Taylor, M.D.[1]

The short-term effects of electroconvulsive therapy (ECT) upon mnestic function are well known. Bilateral ECT results in both retrograde and anterograde amnesia, with both verbal and nonverbal memory adversely affected. The effect is significantly smaller but not insubstantial following unilateral ECT. The degree of deficit is

[1]Departments of Psychology, and Psychiatry and Behavioral Sciences, University of Health Sciences/The Chicago Medical School, North Chicago, IL 60064.

not correlated with clinical improvement of depression, and significant recovery of mnestic function occurs within 1 to 2 weeks after completion of treatment. By 6 months posttreatment, recovery is virtually complete, although some deficit remains for recall of events during the treatment period (Fink, 1979; Harper & Wiens, 1975; Fink, 1977; Squire, 1977; Squire & Chace, 1975). The effects of ECT upon other higher cortical and subcortical functions are less clearly understood, although results from early and more recent studies suggest little if any permanent disability.

Further study is essential, as careful evaluation of cognitive changes associated with ECT has practical and theoretical importance. Treatment decisions clearly necessitate consideration of potential side effects associated with ECT, and delineation of cognitive performance before and after ECT may help to explain possible mechanisms accounting for treatment efficacy, the nature of the dysfunction in depressive illness and, in general, may provide information on brain-behavior relationships. Realization of these goals, however, requires that studies be designed and evaluated with respect to several important issues.

Methodological and Theoretical Considerations

Subject Sample Characteristics

To properly evaluate the cognitive effects of ECT, patient selection must be precise, as there is evidence (Taylor, Redfield, & Abrams, 1981; Abrams, Redfield, & Taylor, 1981) that there are differing patterns of cognitive deficits between the major psychiatric disorders. Nevertheless, several studies use heterogeneous patient groups and include schizophrenics (Horan, Ashton, & Minto, 1980; Small, I.F., Small, J.G., Milstein, & Moore, 1972) who have significant cortical dysfunction (Abrams et al., 1981; Taylor et al., 1981). Diagnostic problems extend to difficulty in evaluating and controlling for severity of psychopathology: Matching groups by depression score alone is inappropriate and should include for comparison other symptoms that form the constellation of the depressive illness so that nonendogenous patients are separately evaluated or excluded from study (Taylor, 1982a). Subject demographic variables (e.g., age, sex, education) are usually controlled, but other important and confounding variables (e.g., medication, previous ECT) often are ignored (Horan, Ashton, & Minto, 1980; Kronofol, Hamsher, Digre, & Waziri, 1978; McAndrew, Berkley, & Matthews, 1967).

Further, evaluation of cognitive effects of ECT is confounded by patients' premorbid ability levels. Cognitive level has been examined only in the immediate pre-ECT period, when the nature of the psychiatric illness itself is likely to impair performance. Lack of change or improvement in cognitive performance after ECT could be due to either a lack of serious neuropsychological effects of ECT, or ECT-induced cognitive impairment associated with cortical dysfunction which is counteracted by improved performance resulting from elevated mood. Educational attainment can be evaluated as an approximate index of premorbid intelligence. Examination of earlier records and/or assessment of vocabulary are more exact.

Cognitive Testing

In evaluating cognitive effects of ECT, it is essential to specify the testing schedule, since effects appear to vary with the number of treatments and the time period between the ECT and the assessment, both for a given ECT and after a course of treatments.

In selecting tests to assess cognitive change, the following standard design features and psychometric criteria should be satisfied: a) acceptable reliability and validity; b) normative data available or easily collectable; c) appropriateness for use with psychiatric patients, as evidenced by previous use with younger subjects, neurological, or other psychiatric samples; d) standardized instructions and procedures to ensure uniformity of administration within and across centers; e) objective scoring procedures; f) reasonable time limits, to allow assessment of multiple abilities within one test session without compromising reliability; and g) appropriateness for repeated testing, so that practice and fatigue effects are minimized, and state-dependent learning factors do not confound the results.

Attempts to relate cognitive changes to neurological function or to etiological theories of

depressive illness require that the tests used meet the following specific theoretical criteria: a) established or suggested sensitivity to neurological disruption, i.e., that there be data on changes with localized or lateralized damage; b) ability to tap "higher order" cognitive functions of the type reputed to be disrupted with ECT or drugs; c) minimal involvement of short-term memory, to minimize performance changes due to memory disruption and maximize ability to see true "cognitive" changes; and d) ability to examine constituent components of complex cognitive functions, i.e., to attribute cognitive changes to specific aspects of processing, or to statistically control the influence of simpler functions on performance on more complex tasks.

Ultimately, it is desirable to determine the nature of the cognitive disruption(s) or improvement(s), i.e., to what extent the processes affected are specifically attention/concentration, speed, perceptual-motor ability, reasoning, synthesis, planning, disorientation, or general cognitive deficit, and tests should be administered that provide such information.

Data Analysis

Studies evaluating effects on a number of correlated tasks with several groups each of small size are plagued by statistical difficulties of high Type I error, nonindependence of comparisons and low power. These problems can be attentuated by using matching procedures and associated statistics, and multivariate analysis (Timm, 1975). Difficulties with matching on pre-ECT cognitive level can be handled with analysis of covariance designs (Cohen & Cohen, 1975).

Some studies (e.g., Kronofol et al., 1978) contain implicit or explicit statements concerning the relationship between cognitive changes and clinical efficacy of ECT, i.e., cognitive improvement is directly associated with relief from depression. In no study has this been adequately tested by correlating cognitive performance with clinical course.

Review of Results Reported

The literature on the adverse effects of ECT most frequently reports transient neuropsychological deficits that occur during the first 30 minutes post-ECT. These include dysphasia after unilateral dominant ECT (Clyma, 1975), and tactile and visual inattentions (Kriss, Blumhardt, Halliday, & Pratt, 1978) and construction dyspraxia following unilateral nondominant ECT. Until recently, most studies have had serious methodological limitations and have examined neurological and perceptual functions, rather than higher order cognitive abilities.

The recent studies reporting more extensive testing of long-term cognitive function have better methodological controls than the older studies, but are still far from optimal. It is possible, however, to evaluate these recent reports in light of the complexities discussed above. The results are confusing and often contradictory, but some tentative findings emerge, along with testable explanations for the discrepancies. In general, the data suggest that little, if any, permanent disability occurs as a result of ECT, and that the treatment may actually improve at least some aspects of cognition, possibly as a result of relief of depression. These conclusions emerge from six relatively large studies attempting to provide methodological controls and using extensive neuropsychological testing. All of these studies, however, are limited by one or another difficulty cited above, including diagnostic problems, varying ECT course and testing schedule, pre-ECT cognitive deficits, small sample size, inadequate test battery, and incomplete data analysis.

McAndrew et al. (1967) compared cognitive consequences of courses of six unilateral right, unilateral left, or bilateral ECT treatments in a group of patients containing mostly depressives. Their results revealed no significant interaction effects, "indicating that pre- and post-ECT test score differences on measures shown to bear a relationship to right as opposed to left cerebral hemisphere dysfunction did not vary as a function of unilateral right, unilateral left, or bilateral electrode placement." The authors interpreted the trends, which were weak at best, as indicating that right ECT was associated more frequently with improvement and less frequently with decrement on right as compared with left hemisphere tasks,

while left ECT was associated more frequently with improvement and less frequently with decrement on left vs. right hemisphere tasks. Post-ECT performance improved on several tests and declined on others, with no apparent pattern. Interestingly, performance on the Halstead Category Test, in part a measure of concept formation, improved post-ECT in all three groups, perhaps as a result of mood elevation. Surprisingly, there were no differences in cognitive change between unilateral and bilateral ECT groups.

Small et al. (1972, 1973) examined cognitive effects of different kinds of somatic treatment, including unilateral left and right and bilateral ECT. A heterogeneous group of patients was tested on a neuropsychological test battery immediately after a treatment of five ECTs, and then again 60-90 days later. Although important details of the methods and results are omitted from the reports, in general it appears that right ECT was associated with immediate unchanged or improved function, and left ECT was associated with impairment in story memory. Testing at 60-90 days revealed that improvements were sustained and the deficit in the left ECT group eliminated. Performance on the Rod and Frame Test of field dependence was assessed in some patients; mean number of errors was unchanged after ECT. However, analysis of responses with respect to direction of rod displacement indicated that the majority of errors occurred on the side contralateral to stimulation.

Kronofol et al. (1978) examined the effects of differing amounts of left and right unilateral ECT in depressed patients. Their data indicated that the small deficits seen after the first ECT were mostly eliminated by the eighth ECT, with the possible exception of verbal fluency, a left frontal function (Benton, 1968; Milner, 1967). The authors stated that, "Neuropsychological tests showed that the right hemispheric functions were more frequently abnormal as compared to left hemispheric (dominant) functions in the pre-ECT tests. ECTs delivered to either the right or left side improved right hemispheric functions when the depression was ameliorated . . . in depression right hemispheric functions are initally disturbed and ECT, instead of being deleterious to these functions, tends to improve them." These interpretations, however, are difficult to defend: only one (of eight) of the increases in right hemisphere performance was significant; normative data were not reported, so there is no way to assess the abnormality of right hemispheric functions pre-ECT; correlations between cognitive improvement and depression amelioration were not reported; depression was relieved with both left and right ECT, whereas no right hemisphere cognitive function was significantly improved with left ECT (and one left hemisphere ability was significantly impaired); differences between left and right ECT groups on some pre-ECT cognitive measures and depression score were not tested statistically; direct comparisons were not made between right and left unilateral ECT groups.

Horan et al. (1980) compared unilateral right and bilateral ECT in two heterogeneous patient samples; testing was conducted 6 to 8 hours after the last of a series of three ECTs. In both samples, performance on the Knox Cube Imitation Test (a sequential, presumably left hemisphere task) was significantly improved. In the one sample where other tests were administered, Vocabulary was impaired in the bilateral group and Form Assembly was impaired in both the unilateral and bilateral groups. The authors suggested that since improvement was specific to the sequencing test, it did not reflect change due to relief from depression, but rather the facilitation or enhancement of left hemisphere sequencing operations with the partial suppression of the right hemisphere accomplished with ECT. Although this explanation fits the data for both left and right hemisphere tasks, it is incompatible with data from their own and other studies showing unchanged or improved performance on some right hemisphere tasks (Kronofol et al., 1978; Small et al., 1972) or failing to show improvement on some sequencing tasks (Kronofol et al., 1978) after right ECT.

Weeks, Freeman, and Kendell (1980) examined prolonged effects (up to 6 months post-ECT) of nondominant unilateral and bilateral ECT in depressed patients. In general, the results indicated no deficits and some improvement with unilateral nondominant ECT at both 1 week post-ECT and later, and small immediate deficits with bilateral ECT that, with the possible exception of memory, cleared up by 6 months post-ECT. Details of these results are difficult to interpret, since pre-post ECT comparisons are made only for the 1-week assessment. At later assessments,

both ECT groups are compared to non-ECT and normal controls. Examination of the data provided indicates that in the unilateral group, both psychomotor speed and cube analysis performance showed significant improvement at 1 week, and performance on a test of short-term attention and concentration was at normal levels by 4 months.

On scales of depression, both ECT and non-ECT groups improved significantly, suggesting that the similar cognitive performance of the groups was due in part to relief from depression. This finding is surprising, since there were no significant differences between groups in amount of medication taken at any stage, raising the possibility that the non-ECT group consisted of more reactive depressives who get well over time without treatment (Taylor, 1982b), an interpretation supported by the significantly greater impairment of the ECT group (as compared to the non-ECT group) on pretreatment cognitive performance.

In a related but less extensive study examining cognitive functioning and ECT, Cohen, Berent, and Silverman (1973) administered the Rod and Frame Test to a group of depressed patients pre-ECT and 5 hours after a single unilateral left, right, or no ECT. Performance was enhanced following right ECT and impaired following left ECT, with no change in the control group. These results led the authors to speculate about "two cognitive controls of attention deployment." The scanning control, related to extensiveness of sampling stimuli, was suggested to be mediated by structures of the right hemisphere. In contrast, the field articulation control—the sorting-out of elements of the field—was proposed to be related to left hemisphere structures.

The studies reviewed above differ in a number of methodological and theoretical variables, several of which could account for the differing conclusions. These include patient sample, sample size, number of ECT treatments. time between ECT and testing, pre-ECT cognitive performance, nature of control group, tests administered, analyses performed, and interpretation of results.

Time Course

The three studies examining the time course of ECT (Kronofol et al., 1978; Small et al., 1972; Weeks et al., 1980) address two separate issues: Effects of differing numbers of ECT, and effects of time since last ECT. The results of Kronofol et al. (1978) indicated that deficits which appear after a single ECT treatment may clear up after a course of eight ECTs. This suggests that the deficit seen by Cohen et al. (1973) on the Rod and Frame Test might disappear with continued ECT treatment, and that the changes seen by Horan et al. (1980) after three ECTs might not persist with additional treatment.

Two studies (Small et al., 1972; Weeks et al., 1980) examined changes in cognition as a function of time after last ECT. The results of Weeks et al. (1980) suggest that cognitive functioning improves with time from ECT, so that small deficits present at 1 week post-bilateral ECT are gone 6 months post-ECT, and improvements seen at 1 week post-unilateral nondominant ECT may actually increase later. Similar results are reported by Small et al. (1972) for testing done immediately following ECT and 60-90 days later. It is likely that there is an endpoint to this recovery and maintenance of cognitive function in at least some patients due to onset of another depressive episode with associated cognitive impairment. Except for the studies of Small and colleagues (1972, 1973), there are no investigations which separate out the changes due to relief of depression from effects specific to ECT. Small et al.'s (1972, 1973) studies are difficult to interpret, however, because of confounds between treatment and clinical variables, and unclear methodological procedures.

The period between ECT and test session is an important time course variable not studied. Of the studies reviewed, tests were administered either between 5 and 8 hours post-ECT (Horan et al., 1980; Kronofol et al., 1978), at 24 hours (Small et al., 1972; Small et al., 1973), "within 48 hours" (McAndrew et al., 1967), or at least a week after ECT (Weeks et al., 1980). Some studies of perceptual and cognitive functioning and neurological effects post-ECT report transient deficits that disappear after 30 minutes (Clyma, 1975; Kriss et al., 1976). It is possible, however, that the recovery curve differs for different functions, particularly higher-order cognitive abilities, and perhaps for the left vs. right cerebral hemispheres.

Electrode Placement

There is surprisingly little support for differential cognitive effects by site of electrode placement, except for a tendency for faster recovery (Small et al., 1972; Weeks et al., 1980) and perhaps improved performance (Cohen et al., 1973; Kronofol et al., 1978; Small et al., 1972) from unilateral nondominant ECT. Unfortunately, sample sizes are often too small to see even moderate effects, groups often differ on pretreatment variables, and direct comparisons between groups are rarely made.

In the only study (McAndrew et al., 1967) in which the effects of all three electrode placements were compared on right and left hemisphere tests, there were no significant interactions between pre-post task performance and electrode placement. Conclusions arguing against differential effects, however, need to be considered in light of the small sample size and insufficient power to see effects.

Pre-ECT Cognition

In those studies (McAndrew et al., 1967; Weeks et al., 1980) where abnormality of pre-ECT cognitive functioning can be assessed, scores are found to be low, consistent with reports of impaired cognition in untreated depressed patients (Goldstein, Filskov, Weaver, & Ives, 1977; Wexler, 1980). Additional difficulties in interpreting pre-post differences are due to pre-ECT cognitive differences between ECT groups (Kronofol et al., 1978; McAndrew et al., 1967) or between ECT groups and controls (Weeks et al., 1980). In order to attribute cognitive changes to ECT treatment, it is crucial to consider pre-ECT levels and to have appropriate control groups, which should consist of non-ECT treated depressed patients matched on demographic, illness, and cognitive variables.

Cognitive Tests

Most studies (Horan et al., 1980; Kronofol et al., 1978; McAndrew et al., 1967; Small et al., 1972) claim to use tests that measure right and left hemisphere function and/or general cerebral dysfunction. Unfortunately, the appropriate reliability and validity data are not always provided or even known. Thus, failure to find effects or unreliability of effects reported (including inability to replicate results) may be a function of the measuring instruments rather than ECT effects. For example, Kronofol et al.'s (1978) finding of post-ECT improvement on one right hemisphere test and no change on other putative right hemisphere tests may be due to test unreliability or to different aspects of hemisphere function measured by each test.

Furthermore, studies have rarely used tests which can identify the nature of the possible cognitive changes, or separate component processes of a task. It is possible, for example, that part of the cognitive impairment seen pre-ECT is due to inattention and/or psychomotor retardation associated with depression. If these deficits are eliminated when mood is elevated, then tasks requiring attention and/or speed would show greater improvement post-ECT. The influence of attention and speed would create further problems in interpreting pre-post ECT effects if right and left hemisphere tasks differentially required these abilities. Thus, complete analysis of the cognitive effects of ECT would include evaluation of attention and psychomotor speed, and statistical analysis of the influence of these variables on performance on other tasks.

One of the most problematic areas of neuropsychological assessment and an area rarely examined in ECT studies is frontal lobe function. The frontal lobes have been implicated in planning, organization, ability to categorize and shift mental set, concept formation, creativity and, in general, in higher order cognitive activities (Hecaen & Albert, 1978; Luria, 1973; Warren & Akert, 1964). It is crucial to assess the influence of ECT on these functions, since they are related to important everyday activities. Persistent patient complaints despite empirical failures to find ECT-induced impairment suggest that it is these higher order frontal lobe functions that may be adversely affected by ECT. Interestingly, one of the largest and most stable deficits resulting from ECT is verbal fluency (Kronofol et al., 1978), an ability shown to be subserved by the left frontal lobe (Benton, 1968; Milner, 1967).

Study Proposals

The inconclusive evidence of cognitive effects of ECT discussed above suggests that further studies be conducted that incorporate changes in study design to allow for more definitive results. Our analysis of the literature, and methodological and theoretical concerns, leads to the following suggested guidelines for designing such studies.

Subject Sample

To attribute pre-post ECT cognitive changes to the treatment, it is crucial to control for the effects of the depressive illness, preferably by matching the ECT group on demographic, illness, and cognitive variables to another group of depressive patients receiving alternative treatment or no treatment. Attempts should be made, where possible, to restrict the sample to endogenous depressives.

Testing Schedule

Since cognitive effects of ECT appear to vary with number of treatments (Kronofol et al., 1978) and time between treatment and assessment (Small et al., 1972; Weeks et al., 1980), it is desirable to test patients before ECT, after one ECT treatment, immediately after a course of six to eight treatments, and longitudinally (perhaps through a period of maintenance) for several months.

Test Battery

The suggested test battery takes approximately 3 hours to administer and is designed specifically to measure potential long-term adverse effects of ECT on higher cognitive function. The tests chosen satisfy the technical criteria specified earlier, and derive from extensive literature on ability testing in normal populations (e.g., Ekstrom, French, and Harman, 1976; Hakstian & Cattell, 1976; Wilson, DeFries, McClearn, & Vandenberg, 1975), and assessment of cognitive changes in clinical neurological populations (e.g., Benton, 1968; Hecaen & Albert, 1978; Jones-Gotman & Milner, 1977; Luria, 1973; Milner, 1963; Milner, 1967; Newcombe, 1969; Rosvold, Mirsky, Sarason, et al., 1956; Teuber & Weinstein, 1956; Warren & Akert, 1964; Warrington & James, 1967) and in drug-treated groups (Harshman, Crawford, & Hecht, 1976; Müller-Oërlinghausen, Bauer, Girke, Kanowski, Gonçalves, 1977). The battery also meets the theoretical concerns expressed earlier and has the capacity to provide closure on unresolved issues of ECT-induced cognitive effects. In particular, tests were selected to allow examination of the influence of attention and psychomotor speed on other cognitive functions, to see differential localization/lateralization effects, and to tap more extensively frontal lobe function.

The Table displays the individual tests recommended, and some relevant technical and theoretical information, including cognitive function measured, reliability and validity, and suggested neurological involvement or drug effect. Further details may be obtained in the references cited, or from the authors.

Conclusions

Although available data suggest that ECT does not result in long-term non-mnestic cognitive disruption, qualifications about possible adverse effects are necessary due to incomplete assessment and inadequate methodological and theoretical controls of past studies. Investigations designed according to guidelines suggested above should help delineate whatever effects may be present.

In particular, the following general set of questions may be answered: What is the nature and extent of the adverse non-mnestic cognitive effects of ECT, and are they prolonged, related to number of treatments, electrode placement, clinical course or the pathophysiology of depressive illness? Should adverse non-mnestic cognitive effects occur, what do these effects indicate about neurological correlates of cognitive functioning, and the mechanisms by which these functions may be affected by depressive illness and somatic therapy?

Table

Suggested Cognitive Battery

Test	Ability Measured	Reliability	Suggested Neurological or Drug Effects
Timed Sentence Writing	Motor speed		
Number Comparison Test	Perceptual speed	.70 - .82	↓ with lithium
Continuous Performance Test	Attention	.74 - .90	↓ with brain damage (various types)
Wisconsin Card Sorting Test	Abstract categorization and ability to change set		Frontal lobe
Analogies	New concept formation		
Logical Inference Test	Logical verbal reasoning	.57 - .78	Left hemisphere; ↓ with marijuana
Reading Comprehension Test	Reading comprehension		Left hemisphere; Some minimal ability in right hemisphere
Originality	Creativity	.74	Frontal lobe for fluency aspect
Word Beginnings and Endings Test	Word fluency	.68 - .71	Left hemisphere especially left frontal
Thing Categories Test	Ideational fluency	.59 - .74	Left hemisphere; interaction of left and right hemispheres
Design Fluency	Figural fluency		Right frontal, right frontocentral
Gollin Figures	Speed of closure		Right hemisphere temporal or parietal; ↑ with marijuana
Embedded Figures Test	Disembedding		Left and right hemisphere, especially left Similar test — ↓ with left ECT, ↑ with right ECT
Copying a Geometric Figure	Constructional ability		Right parietal
Finger Tapping	Fine motor regulation		Contralateral premotor frontal

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Convulsive Therapy: A Risk-Benefit Analysis

Max Fink, M.D.[1]

Since its development in 1934, convulsive therapy has been a center of controversy. It has been applied in many conditions, both in the mentally ill and in patients with physical disorders. The reports vary from anecdotal testimonials and acrimonious diatribes on the one hand, to cautious, well-controlled, independent assessments on the other. To the welter of data, two additional factors emerge to make an assessment difficult—the fluctuating history of enthusiasm and disparagement, and changes in the technique and instrumentation of the treatment. Much of the controversy is highlighted and extensively reviewed in recent publications (Kiloh, 1977; APA, 1978; Fink, 1979; Breggin, 1979; Palmer, 1981; Kendell, 1981).

While convulsive therapy has salutary effects in a variety of conditions, the effects in severe depression are the best documented and are the basis for its continued clinical use. In evaluating the treatment, one is inclined to use the data from the 50-year history of the therapy, despite an awareness that treatments administered in the first decades differed significantly from present practice. But present practice also varies, for as new developments are tested, they are accepted at a varying rate. The introduction of unilateral electrode placement about 1961 showed that complaints of amnesia could be sharply reduced, but doubts as to the efficacy of these modifications are the basis for the continuing controversy. The introduction of succinylcholine in 1953 soon became part of standard academic practice, but its use is still controversial among practitioners who administer the treatments in outpatient settings or patient's homes. The present assessment of efficacy and risks is based on the data of the past two decades, with an emphasis on the use of electroconvulsive therapy (ECT) in the treatment of melancholia, with due regard for the most widely accepted practice as to safety and a reduction of unpleasant sequellae.

[1]Department of Psychiatry and Behavioral Science, School of Medicine, State University of New York at Stony Brook, Long Island, NY 11794. Supported in part by USPHS Grant MH-35518 to the International Association for Psychiatric Research, Inc., St. James, NY 11780.

This review assumes ideal conditions as to selection of cases, administration of treatments, monitoring of side effects, and the training of the therapists. The wide latitude in experience in ECT (and even in the alternate therapies) is surely a principal factor in the outcome of a therapeutic trial, particularly one as complex as convulsive therapy. From a practical point of view, this assessment may be idealized, and may be true only for those patients who are fortunate to be treated by therapists who maintain a sufficient interest in this therapy to maintain their skills for optimal performance.

Efficacy

Convulsive therapy rapidly and efficiently relieves the symptoms of melancholia, regardless of type or duration. It is as effective, and often more so, than pharmacotherapy, and is clearly superior to other therapies in these conditions. The reduction in mortality is a particularly compelling observation, making the risk of suicide an important indication for ECT (Kiloh, 1977; APA, 1978; Fink, 1978a, 1979; Avery & Lubrano, 1979; Kendell, 1981).

Many patients with endogenous depression fail to respond to tricyclic antidepressant drugs, even under the optimized conditions of blood level monitoring for adequacy of dosing. Yet, many of these respond rapidly to ECT. These patients are usually described as being depressed psychotic patients with delusions (Hordern, Holt, Burt, & Gordon, 1963; Glassman, Kantor, & Shostak, 1975; Avery & Winokur, 1977; Davidson, McLeod, Kurland, & White, 1977; Kantor & Glassman, 1977; Nelson & Bowers, 1978; Minter & Mandel, 1979 a,b; Kaskey, Nasr, & Meltzer, 1980; Charney & Nelson 1981). The diagnosis of psychotic depression provides a second compelling indication for the use of ECT.

Catatonia is a syndrome that is particularly responsive to ECT. While it is often classified as a subtype of schizophrenia, it is also a feature of severe infectious diseases and manic-depressive psychosis (Abrams & Taylor, 1976; Taylor & Abrams, 1977; Abrams, Taylor, & Stolurow, 1978). Catatonic patients may also exhibit dysregulation of cortisol metabolism in a fashion that is characteristic of some subtypes of

depressive psychosis (Dysken et al., 1979; Greden & Carroll, 1979). With ECT, this dysregulation rapidly normalizes as the clinical condition improves, suggesting an intimate connection in pathophysiology betweeen the ECT responsive forms of depressive psychosis and catatonia (Fink, 1981).

ECT was introduced as a treatment for schizophrenia, but the efficacy and ease of administration of the antipsychotic drugs, introduced in the 1950s, led to their preferential use. use. But doubts linger that perhaps ECT was discarded too soon. While recent reviews of the literature find little support for its use in such patients (Fink, 1978 a,b; Salzman, 1980), the published studies comparing ECT and antipsychotic drugs do not meet our present standards, so it is unclear whether there is a defined superiority for the antipsychotic drugs. And, as the reports of the incidence and severity of tardive dyskinesia with the use of psychotropic drugs increase, some clinicians are again asking whether there is a place for ECT in the treatment of schizophrenic patients.

Taylor and Fleminger (1980), in a double-blind trial of ECT in patients with paranoid schizophrenia, compared the results of seizures three times weekly (for 8 to 12 treatments) with those of sham seizures. After six treatments, patients in both the ECT and sham-ECT groups improved, with the change clearly greater in the ECT group. Four weeks later, the control group showed little further change, but the ECT group continued to improve. Only one patient in the ECT group still had a rating of illness, while 9 of 10 controls had scores in the pathological range, demonstrating an efficacy for ECT in paranoid schizophrenic patients who had not responded rapidly to medication. In another study, Ries et al. (1981) describe the successful treatment with ECT of nine schizoaffective patients who had not responded to pharmacologic treatment.

In the first years after the introduction of convulsive therapy, mania was reported to respond favorably, with the number of treatments necessary for recovery to be similar to those needed for depressive states. In succeeding years, the number of treatments needed for a favorable outcome increased until the numbers were equal to those used in the treatment of schizophrenia. The reasons for this change in experience are unclear, but may reflect, perhaps, the introduction of alternate treatments for responsive cases of mania, or a change in clinical typology. Since the introduction of lithium and antipsychotic drugs, the efficacy of ECT in mania has not been examined in a prospective study, although McCabe (1976) and McCabe and Norris (1977) make compelling observations of the efficacy of ECT in retrospective reviews. However, the combined use of lithium and ECT may increase the hazards of an organic mental syndrome (Hoenig & Chaulk, 1977; Remick, 1978; Mandel et al., 1980; Small et al., 1980).

In most other conditions in which ECT has been examined, its efficacy is low. This includes patients with drug addiction, alcoholism, psychopathy, and neuroses. Dotted through the ECT literature, however, there are anecdotal reports of patients with parkinsonism showing marked improvement not only in their symptoms of depression, but also in the motor symptoms (Lebensohn & Jenkins, 1975; Dysken et al., 1976; Asnis, 1977; Yudofsky, 1979; Ananth et al., 1980). Balldin et al. (1980) successfully used ECT in seven bedridden parkinson patients without symptoms of endogenous depression. The patients improved in their motor abilities, sufficient for some to return home. Another recent report finds ECT to lower blood sugar levels among diabetics of recent onset (Fakhri et al., 1980).

On efficacy criteria, ECT is clearly justified in the treatment of patients with endogenous depression, particularly those with delusions or suicidal intent, in those with catatonia, and in some cases of mania, and as a weak alternative in the management of the symptoms of acute schizophrenia.

Safety

The principal risks of convulsive therapy are fracture, organic mental syndrome, missed and tardive seizures, and death. These complications were significant features of the early treatments, particularly those that used pentylenetetrazol for induction. But modern treatment methods, which include anesthesia, oxygenation, and muscle relaxation, reduce the complication rate significantly. Anesthesia and monitoring of the seizures further reduce the incidence of missed

and tardive seizures. Thus, for the present methods of induction, two complications remain — death and amnesia.

Under modern conditions of treatment, death may occur with an incidence of 4/100,000 treatments (Royal College of Psychiatrists, 1977; Fink, 1979). More deaths were reported in the early years, when treatment procedures were less well defined (Turek & Hanlon, 1977; Asnis, Fink & Saferstein, 1978; APA, 1978). A principal factor is the risk associated with anesthesia, although the death rate for ECT and its anesthesia is considerably less than that for anesthesia alone (Fink, 1979). A consequence of the relative safety of modern ECT is the paucity of pathologic material, leaving the issue of persistent brain damage unresolved (Fink, 1977, 1979).

The principal risk of modern ECT is amnesia. Every patient who experiences a grand mal convulsion exhibits amnesia for the event, as well as retrograde amnesia. The amnesia persists for varying lengths of time, depending on the age of the subject, location of the electrodes, intensity of the currents, and the number of prior seizures and their frequency (Harper & Wiens, 1975; Fink 1977, 1979; APA, 1978; Fraser & Glass, 1978, 1980; Summers, Robins, & Reich, 1979). But, performance on memory tasks recovers rapidly, so that within 2 weeks of the last treatment, patients perform as well or better than before the treatment (Dornbush & Williams, 1974; Squire, 1977). The principal objection to ECT is the persistence of this syndrome into the recovery period. In an analysis which the author undertook elsewhere, he suggested that the persistence of an organic mental syndrome was no greater than 1/200 cases and may be reduced further by good treatment practice (Fink, 1979).

Complaints of amnesia are usually referred to as the basis for beliefs that persistent brain damage ensues from a course of treatment. Those authors who profess this view with the most energy confuse the data of the early years of treatment, when anesthesia, oxygenation, and modern electrode placements and currents were not used, with our present practice (Friedberg, 1976; Breggin, 1979).

Depressive illness alone, without ECT, is associated with impairment in cognitive functions (Henry, Weingartner, & Murphy, 1973; Sternberg & Jarvik, 1976; Strömgren, 1977). Depressed patients have decrements in short term memory functions, which improve as they recover from their illness with antidepressant drug therapy or ECT.

Even this complaint of amnesia may be significantly reduced by the use of minimal currents and unilateral electrode placements. Amnesia is significantly reduced if the electrodes are placed over the nondominant hemisphere (d'Elia, 1970; d'Elia & Raotma, 1975; Squire & Slater, 1978; Fink, 1979; Strömgren et al., 1980; Kendell, 1981). Further, in the early studies of the selection of currents to induce a seizure, the amnesia was less in treatments which used brief stimulation methods (Liberson, 1953). Interest in the use of these modified currents was recently revived by Valentine, Keddie, and Dunne (1968) and Weaver and his coworkers (1976, 1978, 1979). Ongoing studies by Mandel and by Weiner using such currents suggest that there is indeed a reduction in cognitive defects with their use.

The efficacy of ECT is reflected in the presence of a seizure, and is not dependent on its mode of induction or other characteristics of the convulsion (Ottosson, 1960; d'Elia & Raotma, 1975; Fink, 1979). There has been much recent interest in whether the seizure is indeed necessary, and in four studies which have recently been reported from Great Britain, there is reasonable assurance that improvement is more rapid and more secure with seizures than with sham seizures (Palmer, 1981; Kendell, 1981).

Another complication, more prominent in the past than the present, is that of recurrent spontaneous seizures. The analogy to a kindling phenomenon has stimulated interest in this possibility, but a recent survey of 166 patients who had received more than 2,700 treatments revealed four patients who developed spontaneous fits after a course of ECT, and in only two was it likely to be a proximal cause (Blackwood et al., 1980). In kindling, there is a progressive decrease in the threshold for a seizure, while in ECT, the amount of current needed to induce a seizure generally increases (Green & Costain, 1981). In studies of the kindling phenomenon, anesthesia, particularly the use of barbiturates, is prophylactic for the recurrence of spontaneous seizures. The routine use of anesthesia remains a principal barrier to this complication.

The efficacy of ECT can be sustained without a reduction in therapeutic efficacy and with minimal effects on cognition by proper attention to anesthesia, oxygenation, electrode placement, selection of currents and current dosage, and monitoring. If these observations are put to routine use, then the safety of ECT, particularly with regard to the development of amnesia, will be evaluated more optimistically than at present.

Alternate Treatments

The risks of tricyclic antidepressants are not well defined, although they may be severe. Cardiovascular complications, particularly hypotension and disabling arrhythmias, are recognized with increasing frequency. Death by suicide using tricyclic compounds is frequently reported, although surveys of their incidence are not available. The onset of the therapeutic response is usually delayed, with the standard reference works suggesting that a minimum of 7 to 14 days are required for antidepressant efficacy. In older patients, the anticholinergic effects of tricyclic compounds may be associated with dry mouth and difficulty in urination and in reading (Klein & Davis, 1969; Hartshorn, 1974; Stimmel, 1979).

Avery and Winokur (1976, 1977, 1978) make a strong case for the safety of ECT compared to alternate therapies for depressive psychoses. They find lower suicide death rates in ECT-treated patients. This is also true for the efficacy of ECT in depressed patients with psychotic delusions (Hordern, Holt, Burt, & Gordon, 1963; Glassman, Kantor, & Shostak, 1975; Avery & Winokur, 1977; Davidson, McLeod, Kurland, & White, 1977; Kantor & Glassman, 1977; Nelson & Bowers, 1978; Minter & Mandel, 1979 a,b; Kaskey, Nasr, & Meltzer, 1980; Charney & Nelson, 1981).

The use of monoamine oxidase inhibitors is also restricted by hypertensive crises, cardiovascular and hepatic toxicity, and the interactions of these compounds with foodstuffs, tricyclic antidepressants, and some drugs used in common medical practice (Hartshorn, 1974). Their efficacy is low in depression, although recent studies of their use in neurotic anxiety states are more optimistic.

Comparisons with treatments for other mental illnesses are more difficult. In mania, the efficacy of lithium and the phenothiazines is well defined, but the risks of mortality, blood dyscrasia, organic psychosis, tardive dyskinesia, and other neurologic sequellae must be considered (Klein & Davis, 1969; Gershon & Shopsin, 1975). Lithium therapy has been associated with adverse effects on memory function (Schou, 1968; Kusomo & Vaughan, 1977). In a historical comparison of ECT and lithium, McCabe (1976) found the complications of lithium to be as severe as those for ECT.

In schizophrenia, the complications of ECT depend on the number and frequency of the treatments. Higher dosages are more effective, but the larger number of treatments increases the probability of persistent amnesia and spontaneous seizures. The hazards of antipsychotic drugs are also well defined, particularly tardive dyskinesia, hepatic dysfunction, lenticular opacities, and blood dyscrasia. Despite these hazards, pharmacotherapy seems to have significant advantages over ECT in chronic cases, particularly since maintenance therapy is more easily provided by the drug therapies.

ECT is, at the least, as effective as tricyclic antidepressants, and significantly superior to amine oxidase inhibitors and the various psychotherapies, in the treatment of the severe mentally ill. The latter therapies are particularly hazardous, since death by suicide is an everpresent feature of severe depressive illness.

Consequences of Non-Use of Treatments

Before a nihilistic attitude toward the use of convulsive therapy in the severely mentally ill is adopted, it is useful to consider the natural course of these illnesses before ECT and the drug therapies were introduced. During the 20th century, the number of mental hospital beds escalated until 1955-1960; since then, the number of beds for the hospitalized mentally ill has been sharply reduced. Records of these earlier periods describe many patients with depressive psychoses, mania, and schizophrenia who remained ill for decades. ECT was an important factor in the reduction of hospitalization periods to less than 6 months, and the increase in discharge rates to

80% (Huston & Locher, 1948 a,b), and in the reduction in mortality (Slater, 1951). It is difficult to cite suicide rates, but the recent reports by Avery and Winokur (1976, 1977, 1978), McCabe (1976), and McCabe and Norris (1977), reviewing the data from earlier periods, find greater efficacy, better discharge rates, fewer deaths and suicides, and shorter hospitalizations for patients treated with ECT and/or adequate doses of drugs than alternate treatments, usually milieu and the psychotherapies.

Some recent recollections by therapists who lived through that era of transition reflect on the remarkable effects of their introduction (Post, 1978; Rollin, 1981). A recent report by the scientists at the National Institute of Mental Health Clinical Center cites the successful treatment by ECT of nine cases in 6 years (Paul et al., 1981). There is some discrepancy in attitude when a major educational and research center finds so few cases for this treatment, a treatment which was more successful than a wide range of prior therapies. Similar anti-ECT bias must exist at other centers, particularly those public mental facilities which seem to treat less than 1% of their admissions, while university affiliated centers seem to find up to 5% of admissions to warrant ECT (Asnis, Fink, & Saferstein, 1979). The discrepancy in usage surely reflects political, economic, ideological, and experiential factors, but it does patients little service to be admitted to an institution which has restricted the range of treatments for nonmedical reasons, and to be denied the benefits of an otherwise useful treatment.

Conclusion

The benefits of the use of ECT clearly outweigh the risks and provide a clear indication, above all alternate treatments, for patients with psychotic depression. In these patients, and in those with suicidal risk, ECT is the treatment of choice. This is particularly true for patients with delusions or catatonic features.

A case may be made for the use of ECT in patients with mania and acute schizophrenia, but the indications are less clear, and the usefulness of alternate therapies is sufficiently well defined to warrant their initial use. When the treatment response is delayed, or where compliance for medication treatments is compromised, ECT is an effective and safe alternative.

In schizophrenia, the use of ECT is limited to those patients in whom pharmacotherapy has been unsuccessful. The use of ECT in all other conditions is poorly documented, and its use should be undertaken in research settings, under research protocols.

When the decision to use ECT is made, each patient deserves the full use of modern methods, including anesthesia, oxygenation, muscle relaxation, and the modifications of the induction procedure which minimize persistent effects on brain function. These include the use of unilateral nondominant electrode placements, and/or minimal current instruments. Pretreatment sedation should be minimized, to assure an adequate seizure. Seizures should be monitored, and those which are shorter in duration than some standard (we use 25 seconds) should be immediately repeated. Finally, treatments should be given in settings where the equipment and trained personnel for the emergency management of complications are readily available. In the further management of depressed patients, maintenance drug therapy with tricyclic antidepressants (or their equivalents) should be considered for at least 8 weeks, and probably for 6 months.

Finally, it is time that ECT is clearly recognized as a major treatment in psychiatry, similar to a surgical procedure, and it should be used only by therapists with demonstrated skills who maintain its active practice. Its occasional use, and its unsupervised use by trainees and physicians without special psychiatric skills, is not to be condoned. Only when therapists understand that ECT is a complex procedure, requiring special skills, and when they respect the dignity of their patients not to apply ECT except under optimal conditions, will ECT assume its proper role as a principal treatment of selected cases of the severely mentally ill.

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The subject headings from Index Medicus were selected to reflect significant current interest of the international scientific community. Some nonrelevant citations may appear, and some relevant ones may be absent, but this is usual for machine-generated searches.

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Comments and suggestions are invited.

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Contributions and inquiries should be sent to:

Allen Raskin, Ph.D.
Editor-in-Chief

Lillian Altman
Managing Editor

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ADDENDUM

The October 1981 issue of the *Psychopharmacology Bulletin* (Vol. 17, No. 4, p. 9) included a report on the Clinical Research Center at the Western Psychiatric Institute and Clinic (WPIC) of the University of Pittsburgh Medical School. This report did not include a full description of one of the projects at WPIC, the National Institute of Mental Health (NIMH) Treatment of Depression Collaborative Research Program. This program was initiated and designed by the staff of the NIMH Psychosocial Treatments Research Branch. The program is funded by Cooperative Agreements with the Psychosocial Treatments Research Branch and continues to be coordinated by NIMH staff. The collaborating research sites, in addition to the University of Pittsburgh, include the University of Oklahoma and George Washington University. Three sites are involved in training therapists for the program, Yale University, the University of Western Ontario, and Rush Presbyterian St. Luke's Medical Center. Also collaborating in data management and analysis aspects of the program is the Perry Point Veterans Administration Cooperative Studies Program.

Meeting Announcements

The Brazilian Geriatrics and Gerontology Society (SBGG) will hold its 6th Congress in Belo Horizonte (Minas Gerais), Brazil on October 17-22, 1982. The SBGG is the only scientific and philanthropic society in Brazil carrying out programs for the elderly population. The congress is open to all people involved in the care of the elderly. There will be lectures, debates, and discussions on subjects in the area of geriatrics and basic and social gerontology. Contact Flavio Aluizio Xavier Cancado, Head of the SBGG, Palacio das Artes, Belo Horizonte, MG, Brazil.

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The 4th Congress of the Latin-American Federation of Geriatrics and Gerontology Societies will be held in Montevideo, Uruguay on October 24-28, 1982.

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20th Annual Meeting of the ACNP — Abridged Proceedings

The Twentieth Annual Meeting of the American College of Neuropsychopharmacology (ACNP) was held in Coronado, California on December 16-18, 1981.

This Meeting annually brings together investigators actively involved in psychopharmacologic research. The papers presented at the sessions are indicative of the state-of-the-art in psychopharmacology in the United States, as well as in some foreign countries.

For those who did not attend the conference, we are again publishing summaries of the presentations given at various sessions. In some cases, not all of the papers were included because they were not received in time. Papers based on poster sessions will be published in Vol. 18, No. 4, October 1982 issue.

Publication of these summaries in the *Bulletin* does not prejudice later publication of the full papers elsewhere.

Positron Emission Tomography (PET) and Cortical Localization: Clinical Studies in Psychiatry and Neurology

Co-Chair: **William E. Bunney, Jr., M.D.**
Adult Psychiatry Branch
National Institutes of Health
Rockville, Maryland

and

Earl Usdin, Ph.D.
Neurosciences Research Branch
National Institute of Mental Health
Rockville, Maryland

best copy available

Positron Emission Tomographic Studies of Epilepsy, Brain Tumors, and Alzheimer's Disease

Thomas N. Chase, M.D.,[1] Rodney A. Brooks, Ph.D.,[1] Robert L. DeLaPaz, M.D.,[2] Alessandro Denaro, M.D.,[3] Giovanni DiChiro, M.D.,[1] Raymon Durso, M.D.,[4] Paul Fedio, Ph.D.,[1] Norman L. Foster, M.D.[1] Robert M. Kessler, M.D.,[5] Paul L. Kornbilth, M.D.,[1] Conrad V. Kufta, M.D.,[1] Ronald G. Manning, Ph.D.,[5] Michael E. Newmark, M.D.,[1] Nicholas J. Patronas, M.D.,[1] Roger Porter, M.D.,[1] Susumu Sato, M.D.,[1] Barry H. Smith, M.D.,[1] and William H. Theodore, M.D.[1]

Clinical measurements of local rates of glucose metabolism provide an important new approach to the non-invasive study of human central nervous system function. This procedure, adapted from a model developed by Sokoloff and coworkers (Sokoloff et al. 1977) involves the intravenous administration of 18F-2-fluoro-2-deoxy-D-glucose (FDG) whose phosphorylated metabolite accumulates in brain cells in proportion to their rate of glucose utilization (Reivich et al. 1977; Phelps et al. 1977; Reivich et al. 1979). A positron emission tomography (PET) scanner provides maps of the regional concentration of the radioactively labeled tracer throughout the brain (Ter-Pogossian et al. 1975; Kuhl et al. 1977; Phelps et al. 1978). Since the local metabolic rate for glucose appears to correlate with neuronal firing rates (Sokoloff 1980) as well as with several aspects of normal brain function (Greenberg et al. 1981; Huang et al. 1980; Phelps et al. 1979, 1981), the FDG technique may contribute substantially to the study of neurologic disease. Recent observations by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) investigators of patients with epilepsy, brain tumors, and Alzheimer's disease will be briefly reviewed.

[1]Intramural Research Program, National Institute of Neurological and Communicative Disorders and Stroke, Bethesda, MD 20205.
[2]George Washington University Medical Center, Washington, D.C. 20037.
[3]Department of Neurology, University of L'Aquila, L'Aquila, Italy.
[4]Boston Veterans Administration Medical Center, Boston, MA 02132.
[5]Department of Nuclear Medicine, National Institutes of Health, Bethesda, MD 20205.

Method

Consenting individuals were admitted to the National Institutes of Health (NIH) Clinical Center for study. FDG was prepared (Ido et al. 1980), with 18F obtained from the Naval Research Center or Brookhaven National Laboratory as previously described (DiChiro et al., submitted). By means of bilateral upper extremity catheters, up to 5 mCi of FDG was rapidly injected intravenously while serial "arterialized" venous blood samples were obtained from the opposite extremity for the determination of FDG and glucose concentrations. Following isotope administration, patients were kept quietly in the recumbent position to minimize external stimuli. PET scans were performed by an Ortec ECAT II tomograph having a spatial resolution of approximately 1.7 cm^3 in the image plane and 1.8 cm in the axial direction. Scanning, usually at 6 sequential levels parallel to the canthomeatal plane, began about 30 minutes after FDG infusion. Calculation of local metabolic rates for glucose in mg per 100g of tissue per minute (Huang et al. 1980; DiChiro et al., submitted) was based on rate constants determined from normal young adults. In some studies comparisons were made between the metabolic rate for glucose in selected brain regions and corresponding contralateral zones.

Epilepsy

PET scanning following FDG adminstration helps identify local alterations in cerebral function in patients with complex partial seizures (Newmark et al. 1981). Previous studies using this method suggested that individuals with focal seizures, when studied interictally, evidenced a region of reduced glucose metabolism that becomes hypermetabolic during a clinical seizure (Kuhl et al. 1980). Subsequent NINCDS investigations have sought to ascertain the usefulness of the FDG technique in patients with diffuse, nonlocalized epileptiform foci, as well as to determine the stability of PET abnormalities in

response to changes in various environmental factors.

All study subjects had refractory complex partial seizures associated with normal neurologic examinations and computed transmission tomographic (CT) scans. Interictal PET scans in patients with unilateral or predominantly unilateral epileptiform discharges invariably revealed an area of hypometabolism. Moreover, three of the four patients studied who had diffuse or bilateral discharges had a discernible interictal hypometabolic focus.

PET results were substantially influenced by clinical seizures occurring shortly after FDG injection. Individuals with seizures during the 30-minute period of FDG uptake were found to have a hypermetabolic focus in the area that was hypometabolic interictally. A comparison of interictal and ictal scans in such patients allowed a substantially better localization of the seizure focus than either ictal or interictal scans alone. Interictal PET foci did not, however, appear to be affected by the frequency of seizures between scans or the frequency of spike discharges occurring during the 30 minutes following FDG injection. Changes in anticonvulsant medication also failed to modify PET scan results. Similarly, alterations in the patient's state of alertness had no discernible effect on interictal PET abnormalities.

Brain Tumors

Human brain tumors range in malignancy from slow growing, relatively benign lesions (e.g., Grade I or II astrocytomas) to rapidly expanding, highly invasive neoplasms (e.g., glioblastomas). Although current radiologic techniques often provide useful information, diagnostic uncertainties with respect to tumor grade are not uncommon. Moreover, assessment of tumor recurrence after surgical, radiologic, or chemotherapeutic intervention may be difficult. Since available evidence suggests a positive correlation may exist between degree of malignancy and rate of tumor glycolysis (Macbeth & Bekesi 1962; Wolleman 1972), the FDG-PET technique for quantifying local rates of glucose metabolism may afford a more accurate, noninvasive approach to the clinical evaluation of cerebral neoplasms (DiChiro et al., submitted)

NINCDS studies of over 20 patients with primary brain tumors now indicate that a positive correlation does exist between malignancy grade and metabolic rate as determined by the FDG method (DiChiro et al., submitted). On average, Grade III and IV tumors exhibit twice the metabolic rate of the more benign Grade I and II tumors. It now also appears that clinically successful chemotherapeutic or radiologic treatment may be associated with a reduction in the apparent glucose utilization of these tumors.

Alzheimer's Disease

PET evaluations of patients with Alzheimer's disease may eventually provide insight into the pathophysiology of neuronal degenerative disorders as well as into the localization of major human brain functions (Ferris et al.1980; Foster et al. 1982). Right-handed Alzheimer's disease patients with disproportionate failure of visuoconstructive, language, or memory function were selected for initial study (Foster et al. 1982). CT scans from four individuals in whom constructional apraxia was the predominant cognitive impairment revealed diffuse cortical atrophy without focal abnormalities. PET scans of these patients consistently showed a conspicuous focus of low glucose consumption in the right parietal region. Glucose metabolism in this area of the nondominant hemisphere, classically associated with constructional praxis, averaged 24 percent less than the same region in the opposite hemisphere. This right-left difference significantly correlated with various tests of visuoconstructive function (e.g., Rey copy test, block design). Stimulation of one apractic patient by repetitive spatial tasks during the 30-minute period immediately following FDG injection failed to produce a significant increase in the metabolic rate of this area of hypofunction.

Focal right parietal hypofunction was not found on PET scans from Alzheimer's disease patients who were free of clinically significant constructional apraxia. On the other hand, a patient with global receptive and expressive aphasia out of proportion to his other cognitive deficits had a conspicuous focal area of hypometabolism in the left parietal region. This finding was hardly unanticipated, in view of the well-accepted brain localization of language function as well as the

results of a previous PET study of aphasic patients (Metter et al. 1981). Considering the entire group of nine Alzheimer's disease patients studied thus far, there was a significant positive correlation between degree of language impairment (as evidenced by tests such as the verbal IQ on the Wechsler Adult Intelligence Scale) and absolute left temporal-parietal metabolism or relative left temporal-parietal reduction compared with the same area in the right hemisphere. Four Alzheimer's patients, clinically selected prior to PET scanning on the basis of disproportionate failure of memory, had no significant left-right differences in the temporal-parietal regions which are classically associated with aphasic disturbances. On the other hand, temporal lobe glucose metabolism, especially medially in the hippocampal area, tended to be reduced bilaterally in these individuals compared with other cortical regions or with the hippocampal regions in Alzheimer's disease patients with predominant apractic or aphasic dysfunction.

Concluding Remarks

Results are briefly presented from three ongoing NINCDS studies of neurologic disorders in which the application of the FDG-PET technique now appears exceptionally promising, not only in relation to direct patient management but also to the broad study of normal and disordered human brain function. Conclusions based on the present limited material must remain highly tentative, especially in view of the relatively poor spatial resolution of available scanning equipment, the lack of appropriate normative data, and the uncertain applicability of some assumptions used in the calculation of metabolic rates. Considering the pace of current investigative efforts, it can be confidently predicted that these limitations will appreciably lessen in the near future. Use of other positron-labeled tracers, alone or in combination with FDG, will further enhance the ultimate clinical usefulness of the PET technique.

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Cerebral Blood Flow in Depression and Mania[1]

A. John Rush, M.D.,[2] Michael A. Schlesser, M.D.,[2] Ernest Stokely, Ph.D.,[3] Frederick R. Bonte, M.D.,[3] and Kenneth Z. Altshuler, M.D.[2]

Various investigations suggest patients with affective disorders suffer impairment of higher cortical functions (Ross & Rush 1981). Measures of regional cerebral blood flow (rCBF) provide methods that may potentially tell us, albeit indirectly, about the functional activity and/or capacity of specific regions in the brain. Until recently, such measures were restricted to information derived from lateral views of both hemispheres. Stokely et al. (1980) have developed a single photon emission tomograph method using inhaled 133 Xenon gas that provides views of three cross-sectional brain slices (4 cm apart) with a resolution of 1.7 cm (Lassen et al. 1981).

Twenty-six adult male and female patients, aged 19-69, were evaluated with Research Diagnostic Criteria (Spitzer, Endicott, & Robins 1978), Diagnostic and Statistical Manual-III (DSM-III) (APA 1980), and the 1 mg Dexamethasone Suppression Test (DST) (Carroll et al. 1981). Whenever feasible, subjects ($N = 17$) were studied at two points in time (when acutely ill and later when in clinical remission). Symptom severity was gauged by the 17-item Hamilton Rating Scale for Depression (HRS-D) (Hamilton 1960). Treatment varied across subjects and included electroconvulsive therapy (ECT), tricyclic antidepressants, alprazolam, monoamine oxidase inhibitors (MAOIs), lithium, or haloperidol. Treatment was ongoing when the repeat measurement of rCBF was made for those taking medication. For those receiving ECT, no less than 2, and most typically 5 days, elapsed between the last ECT treatment and the second rCBF determination. Treatment selection was independent of rCBF findings.

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[1]This study was supported in part by grants from The Meadows Foundation and The Biohumanics Foundation.

[2]Department of Psychiatry and Affective Disorders Unit, University of Texas Health Science Center, Dallas, TX 75235.

[3]Department of Radiology and Nuclear Medicine Center, University of Texas Health Science Center, Dallas, TX 75235.

RCBF in ml/100 gm/min was determined using a single photon emission computerized tomographic scanner (Stokely et al. 1980). Values reported were derived from the mid slice for both whole brain and/or right and left hemisphere values separately. The algorithm used to calculate flow is still undergoing revision; thus, the actual numbers shown likely exceed actual flow in all subjects. However, the same algorithm was used in all subjects, so that comparisons between subject groups and within subjects over time are likely to be valid. Controls were gathered from volunteers at the medical center who reported themselves to be free of psychiatric symptomatology, medical illnesses, and medications.

Results

Ten unipolar depressed subjects who were both endogenous by RDC and melancholic by DSM-III were studied (UP-ED). Six Bipolar I or II subjects in the depressed phase (BP-D); four nonendogenous, nonmelancholic, unipolar patients (UP-NED); and six Bipolar I patients in mixed or manic phases (BP-MM) were studied.

RCBF was lower for the UP-ED group ($t = 2.10$, $p < .05$) and higher for the BP-MM group ($t = 2.97$, $p < .01$) compared to controls. The BP-D group did not differ from controls ($t = 0.09$, $p < .50$). Flow in UP-NED patients was higher than controls, although the sample size precludes meaningful statistical evaluation.

A significant *increase* in whole brain rCBF ($N = 8$) was found with treatment and complete clinical response (HRS-D score of 6 or less) in the UP-ED group (paired t-test, $t = 2.62$, $p < .04$). The type of treatment (ECT vs. medication) did not relate to this finding.

RCBF changes in treated BP-D patients were more heterogenous (three showing increases and three with decreases in whole brain rCBF). Two of the three with decreases subsequently relapsed in the following 2 months. No significant pre- or posttreatment differences for the groups as a whole were found (paired t-test, $t = -9.546$, $p < .65$).

Taken together, these data suggest that a) whole brain cerebral blood flow is low in melancholic, endogenous UP patients compared to controls and compared to themselves when later clinical remission; and b) whole brain cerebral blood flow is elevated in BP-MM patients compared to controls. To determine the differential contribution of the left and right hemispheres to these findings, flow rates for each hemisphere, as seen from the mid-slice, were calculated. The increases or decreases in whole brain rCBF found in the above diagnostic groups profoundly involved *both* left and right hemispheres.

While the majority of controls (14/16) showed a very slightly greater flow to the right hemisphere when at rest with eyes open, the majority of all UP-ED, BP-MM, and BP-D patients (13/22) showed a slightly greater flow on the left when acutely ill. This was significantly different from normals by chi-square ($X^2 = 7.26$, $p < .01$).

While both between-group and within-subject comparisons for UP-ED patients suggest that a lower rCBF is found during this illness and between-group comparisons suggest a higher rCBF in BP-MM and a lower rCBF in UP-ED patients, these findings are only preliminary. Samples are small; flow computations are still under investigation; more extensive control data are needed; better controls for age effect and Pa CO_2 are needed; and the effect of medications on rCBF deserves closer scrutiny.

One group (Risberg 1980) suggests no differences between depressed and controls, whereas another group (Matthews et al. 1980) did find a lower left hemisphere flow in their depressed subjects and a trend toward lower right hemisphere flow. While these data demonstrate the feasibility of rCBF determinations by inhaled 133-Xenon, the findings must be replicated.

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Biochemical and Behavioral Studies of Anxiety

Chair: Erminio Costa, M.D.
Preclinical Pharmacology
National Institute of Mental Health
St. Elizabeth Hospital
Washington, D.C.

Convulsive Benzodiazepine Receptor Ligands

Claus Braestrup, M.D.,[1] Erling N. Petersen, Ph.D.,[2] and Mogens Nielsen, Ph.D.[1]

It is generally believed that the benzodiazepine group of minor tranquilizers exert their pharmacological and clinical effects by an interaction with specific benzodiazepine (BZ) receptors located on neurons in the central nervous system (CNS) (Braestrup & Squires 1978).

It was believed that agents that interacted with benzodiazepine receptors would have benzodiazepine-like pharmacological effects. Recently, however, it was observed that the very potent BZ receptor ligand ethyl β-carboline-3-carboxylate (β-CCE) (Braestrup et al. 1980) failed to elicit benzodiazepine-like actions but that β-CCE, on the other hand, antagonized effects of benzodiazepines (Tenen & Hirsch 1980; Cowen et al. 1981). More recently, an imidazodiazepine carboxylic acid ethyl ester has been described (Ro 15-1788) which also antagonizes the effects of benzodiazepines (Hunkeler et al. 1981). These findings indicate that BZ receptor ligands bind in different ways to BZ receptors. Thus ligands may have different efficacies without differences in affinity.

During structural modifications of β-CCE we observed that the corresponding methyl ester, β-CCM [10-50 mg/kg intraperitoneally (i.p.)] and, in particular, methyl 4-ethyl-6, 7-dimethoxy-β-carboline-3-carboxylate (DMCM, Figure) (5-15 mg/kg, i.p.) produced convulsions in mice and rats when given i.p. Convulsions produced by DMCM (15 mg/kg, i.p.) were similar in quality to convulsions produced by bicuculline and pentylenetetrazol.

Convulsions produced by β-CCM and DMCM

[1]Sct. Hans Hospital, DK-4000 Roskilde, Denmark.
[2]A/S Ferrosan, Research Division, DK-2860 Soeborg, Denmark.

DMCM

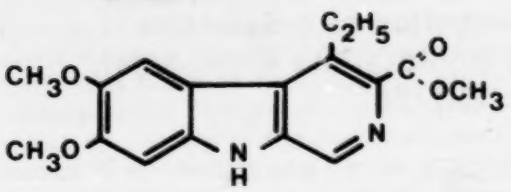

FIGURE. Chemical Structure of DMCM (methyl 4-ethyl-6, 7-demethoxy-β-carboline-3-carboxylate; ZK 90798)

are probably the consequence of BZ receptor interaction for reasons cited below:

1. β-CCM and DMCM have high affinity in vitro for BZ receptors, IC50 values for inhibition of specific [^{3}H]-flunitrazepam (^{3}H-FNM) binding to rat cerebellar membranes are 3 nM and 11 nM, respectively.

2. β-CCM and DMCM occupy BZ receptors in the brain of living animals after systemic administration. The dose that inhibits by 50 percent the BZ binding sites available for [^{3}H]-FNM intraventricularly) (i.v.) is 22 mg/kg (i.p., 35 min) for β-CCM and 4 mg/kg (i.p., 35 min) for DMCM in mouse forebrain.

3. The occurrence of clonic convulsions, tonic convulsions, and death, produced by 15 mg/kg, i.p., of DMCM in mice, can be antagonized by β-CCE (70 mg/kg, i.p.) and Ro 15-1788 [7 mg/kg, orally (p.o.)]. These agents are *not* general anticonvulsants but share the ability to occupy BZ receptors without producing overt pharmacological actions when given alone. Barbiturates and benzodiazepines likewise inhibit convulsions produced by DMCM.

4. Alternative mechanisms of action of β-CCM and DMCM have not been suggested by pharmacological and biochemical studies. When investigated with affinity binding techniques *in vitro*, DMCM, for example, does not interact with serotonin, dopamine (D-2), noradrenaline (α_1), gamma aminobutyric acid (GABA), glutamate, opiate (μ), or cholinergic (muscarinic) receptors.

5. GABA and BZ receptors are functionally coupled at the molecular level. It has been suggested that the effect of GABA agonist on the affinity of a particular BZ receptor ligand for BZ receptors may reflect the pharmacological profile of that agent (Ehlert et al. 1981; Braestrup & Nielsen 1981; Möhler & Richards 1981). Thus, GABA enhances the affinity *in vitro* of one group of BZ ligands, which consists mainly of conventional benzodiazepines (Group I) and this group of ligands exert benzodiazepine like anticonvulsant and anxiolytic activity in animals and man. For ligands in Group II, GABA has no major effect on the affinity of the ligands for BZ receptors, and members of this group antagonize effects exerted via BZ receptors without having overt pharmacological effects when given alone (examples are several β-carbolines and Ro 15-1788). In Group III, GABA agonists reduce the affinity of the ligands for BZ receptors and ligands in this group. For example β-CCM and, in particular, DMCM, have pharmacological effects opposite to those of the benzodiazepines. Thus, β-CCM and DMCM produce convulsions in rats and mice and in addition produce effects in rats that may be interpreted as anxiogenic (Petersen et al., submitted).

The affinity of DMCM for cerebellar BZ_1 receptors *in vitro* in chloride-containing buffer is reduced to 50 percent of the normal value by adding the GABA agonist muscimol (10^{-5}M) to the assay; this effect of muscimol is antagonized by bicuculline (10^{-5}M). The convulsant effect of DMCM and β-CCM is consistent with the BZ receptor/GABA receptor model. Consonant with these conjectures, it has also been observed that DMCM reduces the electrophysiological effects of GABA in cultured spinal neurons from the mouse (J. Lambert, unpublished).

In conclusion, BZ receptor ligands can be divided into at least three groups relating to the coupling between BZ receptors and GABA receptors. Further subclassification according to a chloride channel coupling has also been proposed (Fujimoto et al. 1982). Probably, the BZ receptor can exist in at least two conformations. It was surmised that when Group I ligands bind to the resting state of the receptor, they install a shift in direction of one particular conformational state of the receptor. This new state of the receptor-ligand complex is permissible for chloride channel opening by GABA receptor stimulation. No conformational shift occurs when Group II ligands bind to the receptor. Thus, binding has no overt consequences other than inhibiting access of Groups I and III ligands to receptors. When Group III ligands bind, the receptor attains yet a new conformation which now is inhibitory for chloride channel opening by GABA (GABAergic transmission is reduced). It is not known whether these

two assumedly distinct conformations of BZ receptor exist in equilibrium under normal physiological conditions, or whether the resting state of the receptor, found in normal, undrugged individuals, represents a third conformational state.

It should be noted that the experiments described above were conducted using rat cerebellar membranes. Cerebellum is known only to contain one class of BZ receptors, BZ_1 receptors. The present considerations are not related to a BZ_1/BZ_2 receptor subclassification.

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Benzodiazepine Receptor: Interaction of a Selective Benzodiazepine Antagonist, Ro 15-1788

H. Möhler, Ph.D.,[1] and J.G. Richards, Ph.D.[1]

Introduction

Recently, Ro 15-1788, a representative of a novel series of imidazodiazepines, was found to selectively antagonize all major central actions of benzodiazepines by competitive high affinity interaction with benzodiazepine receptors in the central nervous system (Hunkeler et al. 1981). Ro 15-1788 itself is not pharmaceutically active in doses sufficient to antagonize benzodiazepine actions in animals and man (Darragh et al. 1981; Haefely et al. 1982; Hunkeler et al. 1981; Möhler et al. 1981; Polc et al. 1981). Ro 15-1788 may find therapeutic application as an antidote in cases of intoxication involving overdoses of benzodiazepines, and in anaethesiology for terminating benzodiazepine-induced sedation (Haefely et al. 1982, Hunkeler et al. 1981).

Difference in Receptor Interaction of Benzodiazepine Agonists and Ro 15-1788

Benzodiazepines and the antagonist Ro 15-1788 interact with the same benzodiazepine receptor sites (Möhler & Richards 1981) as shown, for example, by light-microscopic autoradiography (Figure 1). The mode of receptor interaction, however, must be different, since benzodiazepine agonists trigger a biological response while Ro 15-1788 does not. This different receptor interaction is reflected in the different susceptibility of agonists and antagonists to conformational changes of the benzodiazepine receptor. It is known that, *in vitro*, GABA and some other compounds can alter the affinity of the

[1]Pharmaceutical Research Department, F. Hoffmann-La Roche & Co., Ltd., CH-4002 Basle, Switzerland.

benzodiazepine receptors for agonists. The affinity of Ro 15-1788, however, remained unchanged under the same conditions (Möhler & Richards 1981). The failure of Ro 15-1788 to respond to conformational changes of the receptor may reflect its inability to induce a conformational change of the receptor and thereby to trigger a biological response.

FIGURE 1. Autoradiogram of high affinity binding sites of ^{3}H-Ro 15-1788 in a sagittal section of rat brain. The slide-mounted cryostat section was incubated with 1 nmol·l^{-1} of the radioligand for 40 min at 4°C, washed, rapidly dried and then exposed to LKB Ultrofilm® for 14 days at 4°C. White areas correspond to the presence of the radioligand. Note the high density of binding sites in several brain regions, e.g. olfactory bulb (ol, external plexiform and glomerular layers), cerebral cortex (ctx, particularly layer IV), molecular layers of hippocampus (hi), dentate gyrus (dg), and cerebellum (cm). The same distribution pattern was found when the benzodiazepine agonist ^{3}H-clonazepam was used as radioligand.

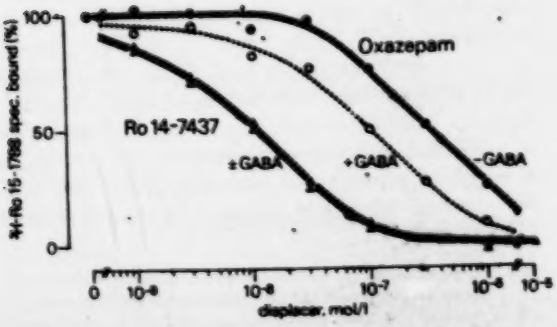

FIGURE 2. ^{3}H-Ro 15-1788 binding in the presence (open symbols) and absence (solid symbols) of 100 μmol·l^{-1} GABA: Inhibition by the agonist oxazepam (circles) and the benzodiazepine antagonist Ro 14-7437 (triangles).

The different receptor interaction of agonists and Ro 15-1788 *in vitro* can be used as a test to distinguish benzodiazepine agonists from antagonists (Möhler & Richards 1981). Their IC_{50} values are determined in ^{3}H-Ro 15-1788 binding in the presence and absence of 100μm .l^{-1} GABA. For agonists but not antagonists, the IC_{50} value in ^{3}H-Ro 15-1788 binding is reduced in the presence of GABA (Figure 2 and Table). For methyl-β-carboline-3-carboxylate, a convulsant benzodiazepine antagonist, the IC_{50} value was even increased in the presence of GABA (Table).

Table

The Inhibitory Potency (IC_{50}) of Various Benzodiazepine Receptor Agonists and Antagonists in ^{3}H-Ro 15-1788 Binding Tested in the Absence and Presence of GABA

	IC_{50}-ratio ± SEM
Agonists	
Flunitrazepam	2.7 ± 0.3
Diazepam	2.9 ± 0.1
Oxazepam	2.7 ± 0.2
Zopiclone	1.6 ± 0.1
CL 118 872	1.6 ± 0.1
Antagonists	
Ro 15-1788	1.0 ± 0.1
Ro 14-7437	0.9 ± 0.1
Propyl-βCC*	1.0 ± 0.1
Methyl-βCC*	0.6 ± 0.05

*β-carboline-3-carboxylate

According to the different types of response to the presence of GABA, several states of the benzodiazepine receptor may be distinguished: The agonist state characterized by an enhancement of the receptor affinity by GABA, the antagonist state in which the affinity remains unaffected by GABA, and an antagonist/convulsant state in which the affinity of the receptor is reduced by GABA.

Model of Ligand-Receptor Interaction

Based mainly on thermodynamic data, a two-step model of ligand receptor interaction was proposed for benzodiazepine receptors (Möhler & Richards 1981),

$$L + R \leftrightharpoons LR \overset{2}{\rightleftharpoons} LR'$$

$$\overset{3}{\rightleftharpoons} LR''$$

in which L is the ligand and R the receptor. Agonists and antagonists participate in reaction (1). Due to their structural properties, agonists but not antagonists can participate in reaction (2) by inducing a conformational change of the receptor to an activated state R′, a prerequisite for the initiation of the agonist drug response. Convulsant receptor ligands induce different conformational change of the receptor reaction (3). Effects opposite to those of benzodiazepine agonists are triggered by these compounds.

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Psychopharmacologic Treatment of Obsessive-Compulsive Disorder

Chair: Dennis Murphy, M.D.
Clinical Neuropharmacology Branch
National Institute of Mental Health
Bethesda, Maryland

Clomipramine Treatment of Obsessive Disorder—Biochemical and Clinical Aspects[1]

Marie Åsberg, M.D.,[2] Peter Thorén, M.D.,[2] and Leif Bertilsson, M.D.[2]

Chronic obsessive-compulsive disorder, a crippling illness in its more severe form, socially disruptive and connected with intense suffering, has long been conceived of as one of the most treatment-resistant conditions known to psychiatry (Goodwin et al. 1969). It is therefore encouraging that a range of new treatments has recently been reported to be effective. Exposure treatment, a variety of behavior therapy, has thus been found to be superior to relaxation procedures (used as a placebo control) in controlled trials (Marks et al. 1980). Among the drugs claimed to be effective are the monoaminoxidase inhibitors (MAOIs), high doses of imipramine (Freed et al. 1972), tryptophan (Yaryura-Tobias & Bhavagan 1977), and clomipramine.

These drugs have different mechanisms of action, but they have one pharmacological effect in common: they potentiate serotonin functions in the brain. Clomipramine, for instance, is the most potent serotonin uptake inhibitor among the tricyclic antidepressants (Carlsson et al. 1969). The MAOIs inhibit enzymatic degradation of serotonin. The serotonin precursor, tryptophan, accelerates synthesis of the transmitter.

These drugs also have (or are claimed to have) antidepressant properties. The tricyclics and the MAOIs have long been used as antidepressants, while tryptophan has been found to potentiate the effect of other antidepressant treatments such as the MAOIs (Coppen et al. 1963), clomipramine (Walinder et al. 1976), and electroconvulsive therapy (ECT) (d'Elia et al. 1977) in controlled trials.

This pattern of effects raises a number of questions. Is the antiobsessive effect (if any) related to the drugs' effect on serotonin neurons? Is it secondary to amelioration of depression in the obsessive-compulsive patients? What is the relationship between depression and obsessive-compulsive disorder? A close connection between depression and obsessive-compulsive disorder has been recognized since at least the turn of the century (Gadelius 1896). Is obsessive-compulsive disorder merely a variety of depression or are the two disorders different manifestations of a common underlying biochemical abnormality?

As yet, there are not sufficient research data to answer any of these questions, but there is some suggestive evidence which will be discussed in this paper. To the authors' knowledge, placebo-controlled trials have only been published with clomipramine, and the discussion will therefore be limited to studies of this drug.

The Controlled Trials

In 1980, three double-blind, placebo-controlled clinical trials of clomipramine in obsessive-

[1]This study was supported by the Swedish Medical Research Council Grant #5454 and by funds from the Karolinska Institute.

[2]Department of Psychiatry, Karolinska Hospital, Stockholm, and the Department of Clinical Pharmacology, Huddinge Hospital, Huddinge, Sweden.

Address correspondence to Dr. Åsberg at the Department of Psychiatry, Karolinska Hospital, S-104 01 Stockholm, Sweden.

compulsive disorder were published. Although their designs differed, they complemented each other in a number of ways.

Thorén et al. (1980a) studied antiobsessive effects in 24 hospitalized patients with severe, chronic (median duration 11 years) obsessive-compulsive disorder. After a drug-free "washout" period, the patients were randomly allocated to one of three treatment groups, clomipramine (150 mg/day divided in three doses), nortriptyline (150 mg/day), or placebo. Treatment was continued on a fixed dosage for 5 weeks. With the exception of occasional low doses of benzodiazepines, no concomitant drug treatment was allowed.

All patients met Research Diagnostic Criteria (RDC) (Spitzer et al. 1978) for obsessive-compulsive disorder. Particular efforts were made to exclude patients with a *primary* depressive illness (as defined by Feighner et al. 1972) from the study. Six patients were diagnosed by the RDC as suffering from a *secondary* depressive condition superimposed on the obsessive-compulsive disorder.

An eight-item subscale for obsessive-compulsive disorder (the OCD Scale, Table 1) derived from the Comprehensive Psychopathological Rating Scale (CPRS; Åsberg et al. 1978) was used to assess effects. After 5 weeks of treatment, clomipramine was significantly superior to placebo, both on the two core obsessive-compulsive symptoms (Rituals and Compulsive Thoughts) and on the entire OCD scale. Nortriptyline effects were in between clomipramine and placebo and did not differ significantly from either. The effect in the placebo-treated group was very small in spite of the supportive hospital environment. The mean score on obsessional symptoms after 6 weeks of placebo treatment was 96 percent of the pretreatment score.

After the controlled phase of the trial, all patients but two were given clomipramine *openly* in a flexible dosage (maximum 225 mg/day). During this phase, behavior therapy, according to the principles laid down by Marks (1973), was also given. On the combined treatment, 12 out of 22 patients could be classified as responders. Clinical and demographic data (including the presence or absence of secondary depression) did not predict response to the combination of clomipramine and behavior therapy.

Table 1

Items of the CPRS-Derived Rating Scales for Obsessive-Compulsive Disorder and Depression

OCD Scale	Depression Scale
1. Rituals	1. Apparent sadness
2. Inner tension	2. Reported sadness
3. Compulsive thoughts	3. Inner tension
4. Concentration difficulties	4. Reduced sleep
5. Worrying over trifles	5. Reduced appetite
6. Reported sadness	6. Concentration difficulties
7. Lassitude	7. Lassitude
8. Indecision	8. Inability to feel
	9. Pessimistic thoughts
	10. Suicidal thoughts

Both scales consist of items drawn from a larger rating instrument, the CPRS (Åsberg et al. 1978). The construction of the two subscales is similar and partially based on the incidence of symptoms in the respective disorders. Note the overlap—half of the items in the OCD scale occur in the depression scale as well.

Marks et al. (1980) compared clomipramine and placebo, with and without exposure treatment. Relaxation procedures were used to control for the time spent with the therapist. The 40 patients studied were all chronic cases with a mean duration of illness similar to those studied by Thorén et al. (1980a). Depressive symptoms were not an exclusion criterion, and pretreatment scores on a depression inventory suggested that only 2 of the 40 patients were not depressed.

The patients were given placebo or clomipramine (flexible dosage up to 225 mg/day given as a single dose at night) on an outpatient basis for 4 weeks. On subsequent admission to hospital, drug treatment was continued without further changes of dosage, and the patients were given either exposure or relaxation sessions. After 6 weeks of psychological treatment, the patients were released from hospital to continue on the drug (or placebo) treatment for another 26 weeks. Final followup was after 2 years.

A series of ratings was used to assess rituals, mood, and general adjustment. Compared to placebo, clomipramine produced significantly more improvement of all these aspects. Severity of the mood symptoms in this patient group predicted response to clomipramine. In the least dysphoric patients only the time spent on target rituals showed a significant advantage of the active drug over placebo. Exposure was connected with an amelioration of rituals. The best effect was obtained in patients who had both drug and

exposure, and the effects of the two treatments appeared to be additive. Compliance with the psychological treatments was better in the patients who had received an active drug.

Montgomery (1980) studied 14 patients with severe and chronic obsessive-compulsive disorder, diagnosed by the RDC of Spitzer et al. (1978). In this study, primary and secondary depressive illness were both exclusion criteria. A crossover design was used, where each patient received either placebo or 75 mg clomipramine (given as a single dose by night) for 4 weeks, and was then crossed over to the other treatment for another 4-week period. Behavior therapy was given once weekly to all patients during the entire trial.

A six-item CPRS subscale for obsessive-compulsive disorder, and a CPRS-derived scale for depression (Montgomery & Åsberg 1979) were used to assess effects. Clomipramine was significantly better than placebo for compulsive thoughts, but not for rituals. There was no significant change in scores on the depression scale with any of the treatments.

Effects on the Serotonin System

Clomipramine is not a "pure" serotonin uptake inhibitor. It is metabolized in the body, and the main metabolite demethylclomipramine is a potent inhibitor of noradrenaline uptake (Träskman et al. 1979). The plasma concentrations of the metabolite are almost always higher than those of the parent compound after oral administration.

Clomipramine's lack of selectivity suggests that the pattern of neuronal effects may be complicated. It is, however, possible to some extent to disentangle the effects of the parent compound from those of the metabolite.

When a monoamine uptake inhibitor is given to a patient, the turnover of the respective amine is changed. This is reflected in a decreased concentration of its metabolite in the spinal fluid. Nortriptyline, for instance, is a preferential inhibitor of noradrenaline uptake and causes a reduction of the noradrenaline metabolite 4-hydroxy-3-methoxyphenylglycol (HMPG) in the spinal fluid (Bertilsson et al. 1974). Zimelidine, which is a relatively selective serotonin uptake inhibitor, causes a decrease in the spinal fluid level of the serotonin metabolite, 5-hydroxyindoleacetic acid (5-HIAA) (Bertilsson et al. 1980).

During clomipramine treatment of depression, both 5-HIAA and HMPG concentrations are reduced. The extent of the HMPG reduction is correlated to the plasma concentration of the demethyl metabolite, and the 5-HIAA reduction is a function of the plasma concentration of the parent compound. The latter association is not linear but U-shaped (Figure 1). Both very low and very high concentrations of clomipramine are associated with a smaller reduction in 5-HIAA than intermediate concentrations (Träskman et al. 1979; Thorén et al. 1980b).

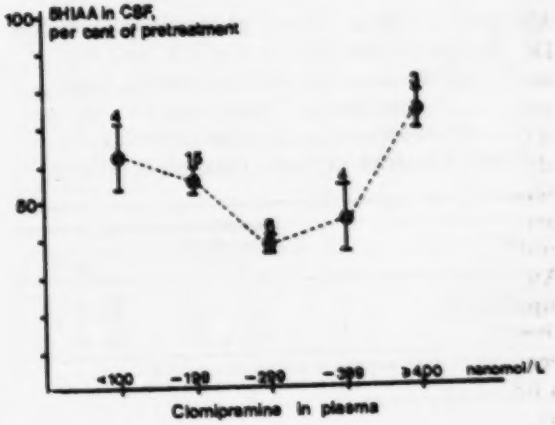

FIGURE 1. Concentrations of 5-HIAA in CSF during treatment with clomipramine (as percent of the pretreatment concentration) in relation to plasma level of clomipramine. Means, standard deviations, and number of patients are given. Both depressed (N = 24) and obsessive-compulsive (N = 8) patients are included.

Thorén and co-workers (1980b) measured spinal fluid concentration of monoamine metabolites before and during treatment with clomipramine, nortriptyline, and placebo in their obsessive-compulsive patients. As expected, nortriptyline caused a reduction in HMPG, clomipramine reduced both HMPG and 5-HIAA, and placebo treatment did not change the metabolite concentrations (Table 2).

The change in 5-HIAA, but not that in HMPG, appeared to be important for the treatment outcome. There was a significant correlation between reduction in 5-HIAA and effect on the two core obsessive symptoms, rituals and compulsive thoughts—the more pronounced the

reduction of 5-HIAA, the better was the effect

This was in contrast to the effect on the rema ing, "dysphoric" symptoms of the OCD scale Table 1), which *increased* with decreasing HM levels, although not significantly (Table 3). t is also in striking contrast to the pattern describ d in endogenous depression, where amelioration dur- ing clomipramine treatment has been found to be correlated to HMPG reduction, but not to c ange in 5-HIAA (Träskman et al. 1979).

Table 2

Changes in Spinal Fluid Concentratio s of the Serotonin Metabolite, 5-HIA the Noradrenaline Metabolite, HM after Three Weeks' Treatment Obsessive-Compulsive Diso der (Eight Patients in Each Treatmen Group)

Treatment	Metabolite conc of pretreatment ntration, percent mean ± SD)	
	5-HIAA	HMPG
Clomipramine	61 ± 14*	68 ± 6**
Nortriptyline	95 ± 16	68 ± 10*
Placebo	91 ± 27	102 ± 8

*Significant reduction compared to pretreatment, p < 0.01.
**Significant reduction compared to pretreatment, p < 0.001.
Data from Thorén et al. (1980)

Thorén et al. (1979) also co related the treatment effect with the plasma concentrations of clomipramine and its metab olite and found a significant negative relatio ship between the parent compound and the effect (once more for the core symptoms only). T is may seem surprising. If the best effect is obt ained with a maximal reduction of 5-HIAA, an d the relationship between clomipramine conc entration and 5-HIAA reduction is curvilinear, he relationship between clomipramine and effe t should also be curvilinear. Closer examina ion of the range of levels found in the obsessiv e-compulsive patients explains the apparent co ntradiction, since almost all patients had plasma l evels in the high range (and thus lie on the right l mb of the U-shaped curve in Figure 1).

A curvilinea r relationship between clomipramine in p lasma and the effect on rituals was indeed found by Stern, Marks, Mawson, and Luscombe in th ir analysis of 20 of the patients studied by Marks et al. (1980). These authors also found a relationship between demethylclomipramine and one effect—the reduction of scores on the Hamilton Depression Scale. This suggests that clomipramine may account for the anti-obsessive effect and the metabolite for the anti-depressant effect. (It may be recalled that depression was not an exclusion criterion in this study.)

Taken together, these findings seem to support the hypothesis of a relationship between amelioration of core obsessive symptoms (in particular, rituals) and a drug effect on serotonin neurons. The number of patients studied is, however, still too small to permit definitive conclusions. The obvious test of the hypothesis would be to try a selective serotonin uptake inhibitor, for instance, zimelidine, in a controlled trial.

Depression, Dysphoria, and Treatment Outcome

The study of Marks et al. (1980) suggests that clomipramine treatment may above all be effective in patients who have affective symptoms in addition to their rituals, while those who are not dysphoric react better to exposure. The study by Thorén et al. (1980a) can hardly be used to investigate the importance of pretreatment depressive symptoms for the effect of clomipramine, since those among the eight clomipramine-treated patients who had high scores on the depression scale also had plasma levels of clomipramine outside the "therapeutic range." The study by Montgomery (1980) cannot be used for this purpose, either, since the patients were given both clomipramine and behavior therapy.

The predictive value of pretreatment depression for the effect of the *combination* of clomipramine and behavior therapy can, however, be evaluated from the two latter studies. Montgomery (1980) explicitly excluded patients with a diagnosis of depression and was nonetheless able to demonstrate an effect, but only on obsessive thoughts. Thorén et al. (1980a) included some patients with a secondary depression, and this diagnosis did not predict outcome. The pretreatment depression scores were 14.2 ± 7.9 in the responders, and 13.0 ± 7.9 in the nonresponders to the combined treatment, a non-significant difference.

Patients who do not receive a *diagnosis* of depression may still have many symptoms, e.g., depressed mood, that are characteristic of depressive illness but are common in other psychiatric afflictions as well. In order to explore further the importance of pretreatment symptomatology, a factor analysis of the 14 item-scores (Varimax rotation, SPSS) was performed on the combined OCD and depression scales from the patients studied by Thorén et al. (1980). In particular, the authors were interested to see whether "depressive" or dysphoric symptoms are highly loaded in the same factor. This appears not to be the case, since classical "depressive" symptoms load on all four factors found in the analysis (Table 3). The first factor, which accounts for about half of the variance, might be labeled an "obsessive" factor, since it is the only one where rituals load strongly. It is also characterized by pessimistic thoughts, reduced sleep, worry, and a *negative* correlation with compulsive thoughts. The second factor might be described as an "anxiety" factor with high loadings for inner tension, concentration difficulties, inability to feel, and reduced appetite, but also for apparent sadness. The third factor appears to be the most "pure" depression factor, with strong loadings for reported sadness, inner tension, suicidal thoughts, and reduced sleep. The fourth factor, finally, could possibly be described as an "asthenia" factor with strong loadings for indecision, lassitude, worry, and compulsive thoughts. Scores on the four factors in patients with and without a diagnosis of secondary depression are shown in Figure 2.

Table 3

Factor Analysis of Scores Given to 24 Untreated Patients with Obsessive-Compulsive Disorder on Items from the CPRS Obsessive-Compulsive Disorder and Depression Scales. Varimax Rotated Factor Matrix

Symptom	Factor 1 (49.9)	Factor 2 (20.7)	Factor 3 (15.7)	Factor 4 (13.7)
Reported sadness	25	24	94	−02
Inner tension	−01	49	55	21
Inability to feel	−12	75	11	11
Pessimistic thoughts	67	21	13	07
Suicidal thoughts	13	−11	49	20
Worrying over trifles	45	26	05	35
Compulsive thoughts	−43	14	26	36
Rituals	59	−03	07	−01
Indecision	10	−16	05	79
Lassitude	02	29	16	61
Concentration difficulties	23	48	−14	−06
Reduced appetite	30	60	24	03
Reduced sleep	62	10	39	03
Apparent sadness	43	36	18	23

The figures within parenthesis are the percentages of variance accounted for by the respective factors.

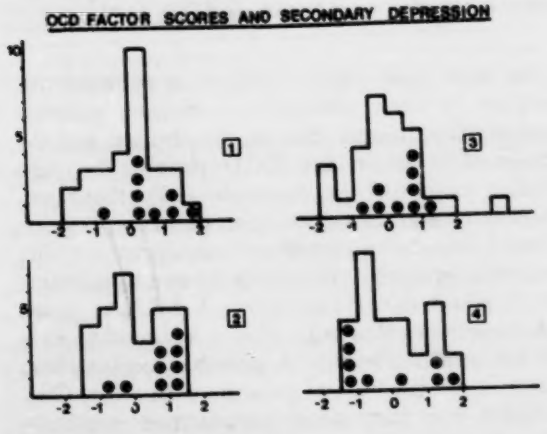

FIGURE 2. Distributions of scores on Factors 1-4 (*see* text) in relation to an RDC diagnosis of secondary depression (filled dots).

Individual factor scores were then related to outcome of the combined treatment with clomipramine and behavior therapy (Table 4, Figure 3). The two "affective" factors, the "anxiety" (2) and "depression" (3) factors correlated positively with outcome, significantly so for Factor 3. The predictive value of the factor scores was low, however and, as seen from Figure 3, some patients with very low scores on the "depression" factor reacted well to the treatment. The outcome of the factor analysis should be regarded with great caution due to the small number of patients ($N = 24$), but would seem to support the contention of Marks and coworkers (1980 and this issue) of a better treatment effect in obsessive-compulsive patients who are also dysphoric.

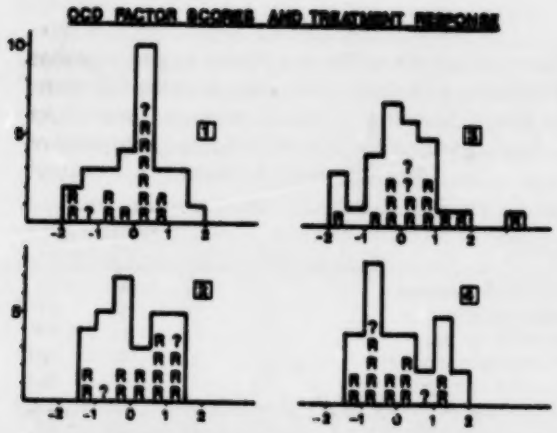

FIGURE 3. Distributions of scores on Factors 1-4 (*see* text) and response category on combined treatment with clomipramine and exposure. R denotes positive response, "?" patients who were included in the pretreatment rating but not given clomipramine plus exposure.

Table 4

Correlations Between Factor Scores and Response to Combined Treatment with Clomipramine and Exposure in 22 Patients with Obsessive-Compulsive Disorder

Factor	Pearson *r*	*p*
1	−0.17	0.38
2	0.36	0.06
3	0.39	0.04
4	−0.27	0.18

Biochemical Disturbances in Depression and Obsessive-Compulsive Disorders

During recent years, research in depression has largely focused on the importance of monoamine neurons and of neuroendocrine functions. Depression, particularly of the endogenous type (melancholia), has been associated with low cerebrospinal fluid (CSF) concentrations of the serotonin metabolite 5-HIAA (*see*, e.g., the review by van Praag 1981; also Åsberg et al. 1982). The low 5-HIAA levels may be characteristic only of a subgroup of patients with melancholia, since the distribution of the metabolite has repeatedly been reported to be nonnormal or bimodal (Åsberg et al. 1976). Melancholia has also been associated with a high frequency of inability to suppress cortisol secretion after administration of dexamethasone (Carroll et al. 1981). In order to elucidate the relationship between melancholia and obsessive-compulsive disorder, it might therefore be of interest to compare distributions of CSF 5-HIAA, and dexamethasone suppression, in obsessive-compulsive disorder and depression.

Figure 4 shows CSF 5-HIAA in patients with melancholia and obsessive-compulsive disorder, and in healthy controls. Only women are shown, since 5-HIAA concentrations differ between sexes, and the group of men with obsessive-compulsive disorder is too small to allow any meaningful comparisons.

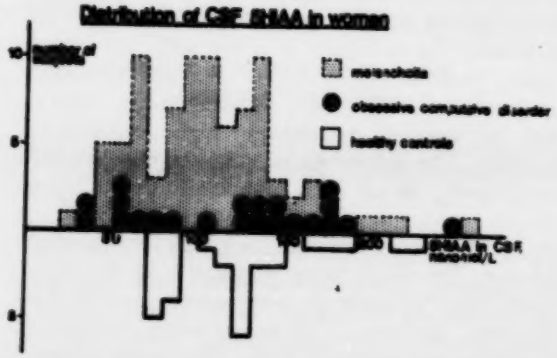

FIGURE 4. Distributions of 5-HIAA in CSF in women with melancholia and obsessive-compulsive disorder, and healthy female controls. Response to clomipramine plus exposure treatment is indicated by R. "?" indicates that response category is not known (*see* legend to Figure 3).

As seen from Figure 4, there is no *mean* difference between obsessive-compulsive patients and healthy controls, but the distribution and the range of levels in the OCD patients is quite similar to that of the depressives. Furthermore, there is a significant association between pretreatment 5-HIAA and response to clomipramine plus behavior treatment. Responders have significantly higher pretreatment 5-HIAA than nonresponders (Table 5). Why this should be so is by no means obvious. A possible explanation, however, might be that patients with a low CSF 5-HIAA may have a low pretreatment synthesis of serotonin, so that inhibition of reuptake still does not result in a sufficient amount of serotonin in the synaptic cleft. This explanation is entirely

speculative but it is testable in principle since, if it were true, addition of tryptophan should lead to an increased therapeutic effect.

Table 5

Pretreatment CSF Amine Metabolite Levels in Responders and Nonresponders to Clomipramine Plus Behavior Treatment

Metabolite	Metabolite Concentration, mean ± SD (nanomol/L CSF)	
	Responders	Nonresponders
5-HIAA	137 ± 39	93 ± 49
HVA	339 ± 100	248 ± 91
HMPG	61 ± 23	52 ± 14

Data from Thorén et al. (1980).

Table 6

Dexamethasone Suppression Tests (DST) in 17 Patients with Obsessive-Compulsive Disorder

	Abnormal $N = 7$ (41%)	Normal $N = 10$ (59%)
Age (mean, SD)	44.0 (12.08)	44.90 (8.69)
Sex (women:men)	6:1	8:2
Depression score (mean, SD)	3.43 (3.40)	3.25 (1.34)
OCD scale score (mean, SD)	7.43 (3.88)	7.85 (2.61)
Obsessive symptoms score (mean, SD)	3.14 (1.65)	3.60 (0.88)
Current medication (clomipramine or drug free)	1:6	2:8
Response to clomipramine (responder ornonresponder)	5:1	7:3

None of the differences between patients with normal and abnormal DSTs are statistically significant.

Dexamethasone suppression tests (DSTs) have been performed in 17 patients with obsessive-compulsive disorder according to the RDC criteria. The tests were performed as recommended by Carroll (Carroll et al. 1981), i.e., 1 mg dexamethasone was given at 2300 hours on Day 1 and blood was drawn for analysis of cortisol (by radioimmunoassay) on Day 2 at 0800, 1600, and 2300 hours. The test was regarded as abnormal if any of these cortisol values exceeded 138 nanomol/L. In seven cases the DST was clearly abnormal. None of the background factors listed in Table 6 differed between patients with a normal or an abnormal DST, not even scores on the depression scale. This outcome would seem to cast some doubt on the specificity of the dexamethasone test for melancholia, at least as that disorder is usually defined. It does suggest, however, that some cases of melancholia and some cases of obsessive-compulsive disorder have a biochemical disturbance in common, in spite of the apparent differences in the clinical picture.

Conclusion

There is now good evidence that clomipramine is indeed an effective drug in the treatment of obsessive-compulsive illness. The presence of dysphoria in the patient may be associated with a better chance of recovery on drug treatment, but its absence does not preclude a good effect. There is indirect evidence that the serotonin effects of the drug are important for its effect on rituals, while the noradrenaline effects may be more important for depression. It may be relevant in the context that a low turnover of serotonin, as reflected in low levels of 5-HIAA in the CSF, has been associated with increased anxiety and increased aggression (Banki 1977; Brown et al. 1979, 1981; Rydin et al. 1982)—two factors that psychoanalytic theory have associated with obsessive-compulsive neurosis.

There is no evidence that the effect of clomipramine declines with time. The long-term outcome of the patients studied by our group has generally been favorable in those patients initially classified as responders (Table 7). Most of these patients are still taking the drug, but two have been drug-free for more than a year without a relapse.

Table 7

Long-Term Outcome of Clomipramine Treatment

	Responders	Nonresponders
Lost to followup	1	2
Recovered or better on clomipramine	9*	
Recovered or better, drug free	2†	
Unchanged		3
Psychosurgery		3
Schizophrenic development		1
Depression (periodic)		1

*Episodic treatment in two cases.
†Both made previous attempts to stop taking the drug, but failed. Both were drug free for more than a year.
Data from Thorén et al. (1980). The follow-up period varies from 5 to 7 years.

There now seems to be enough data on the effect of clomipramine in obsessive-compulsive disorder to allow the formulation of tentative guidelines for its clinical use. In patients with long-standing, severe obsessive-compulsive illness who also are dysphoric, clomipramine appears to be the drug of choice. It can be tried also in patients who are not dysphoric, but the effect is not equally convincing. The treatment effect is not fully apparent until after 5-10 weeks' treatment. Dosage should be individualized. Plasma level determinations may be of help to avoid too high or too low levels, both which seem to be connected with a poorer effect. Combination with exposure treatment is desirable. Treatment should be prolonged, probably over several years. With the exception of dental problems from the reduced production of saliva (which can be avoided by a careful mouth hygiene), no serious long-time side-effects have been described. It is important to assist the patients in recreating meaningful social relationships and activities. A common remark from patients whose symptoms diminish with drug treatment is that they do not quite know what to do with the time that they used to spend on their rituals. A few of our patients have indeed stopped taking the drug, stating that they actually preferred their rituals to an attempt to cope with the demands of an ordinary existence. But for the majority of the responders, the advantages have far outweighed these problems.

Acknowledgment: The assistance of Lisbeth Eriksson in the preparation of this manuscript is greatly appreciated.

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Quo Vadis—Biology of Schizophrenia

Chair: Edward Domino, M.D.
University of Michigan
Ann Arbor, Michigan

Introductory Comments

Edward F. Domino, M.D.[1]

The pathogenesis of each of the schizophrenias is very poorly understood. It is becoming apparent that no single biological theory is adequate to explain the etiology of these diseases. The evidence that current antipsychotic drugs act primarily through blockade of dopamine receptors is most convincing. However, a significant proportion of schizophrenic patients are nonresponders to antipsychotic drugs, a fact well known since their introduction in the 1950s. Even in patients who are drug responders, it seems unlikely that their psychotic symptoms are caused by excessive levels of dopamine or its turnover in the central nervous system. In fact, the clinical biochemical evidence is to the contrary. There is evidence for both supersensitivity as well as subsensitivity of dopamine receptors in some schizophrenic patients. The fact that some dopamine agonists, like apomorphine, in low doses may also temporarily relieve some symptoms of schizophrenia suggests that the discovery of new selective presynaptic dopamine receptor agonists may be a useful therapeutic approach. There is considerable evidence for multiple dopamine receptors in the brain. Our present drugs tend to act on these multiple receptors both pre- and postsynaptically. This tends to blur our thinking regarding their mechanism of action. Obviously, there is a need to discover more specific dopamine agonists and antagonists that act selectively pre- or postsynaptically on each subtype of adenylate cyclase linked and non-linked dopamine receptors. The delayed time course of therapeutic benefit of the antipsychotic drugs suggests that more complex biochemical changes are occurring that involve other neurotransmitter systems as well. It is well known that the increase in prolactin secretion (as an index of dopamine blockade) occurs far more rapidly than the delayed antipsychotic effects of dopamine antagonists. Other putative neuro-

[1]University of Michigan, Ann Arbor, MI 48109 and Lafayette Clinic, Detroit, MI 48201.

transmitters and neuromodulators including the prostaglandins, γ-aminobutyric acid, histamine, acetylcholine, phenethylamines, indolealkylamines, opioid peptides, etc. have all been implicated in schizophrenia. The structural changes in schizophrenic brains, as measured via computerized axial tomography (CAT) scans, as well as the decrease in cerebral cortical glucose utilization, as measured via positron emission tomography (PET) scans, suggests a most complex biology of schizophrenia. Where do we go from here? That is the purpose of the present workshop in which various points of view were discussed by a distinguished panel of speakers who have made important contributions to our knowledge in this field. The workshop was specifically designed to be speculative and provocative, for hopefully it will lead to new directions of research.

Two Dimensions of Pathology in Schizophrenia: Dopaminergic and Non-Dopaminergic

Timothy J. Crow, Ph.D., D.P.M., F.R.C.P., F.R.C. Psych.[1]

The belief that the primary disturbance in schizophrenia is chemical has long been plausible; that it is a disturbance of neurohumoural function is supported by observations that schizophrenic symptoms can be exacerbated in patients and provoked in nonpsychotic individuals by drugs that act on specific transmitters. The psychosis seen in some amphetamine abusers may be indistinguishable from acute paranoid schizophrenia (Connell 1958; Ellinwood 1967). The psychotic changes, like those in schizophrenia, occur in clear consciousness (that is, in the absence of disorientation) and can include first-rank symptoms (certain types of auditory hallucinations, delusions of passivity and interference, thought alienation, and delusional perception). In animals, many of the behavioral effects of the amphetamines have been shown to be due to increased dopamine release from the central dopamine pathways (Randrup & Munkvad 1967), and the psychotic changes in man seem likely also to be associated with increased dopaminergic transmission.

Mechanism of Antipsychotic Effects

Both schizophrenic symptoms and those of the amphetamine psychosis are reduced by neuroleptic drugs. Carlsson and Lindqvist (1963) found that these drugs increase dopamine turnover and suggested this was secondary to blockade of the dopamine receptor. Dopamine-induced activation of adenylate cyclase in the corpus striatum is inhibited by neuroleptic drugs; this inhibition correlates well with antipsychotic potency (Miller et al. 1974) for a range of drugs, though the butyrophenone compounds are somewhat less active than would be predicted from their clinical effects. Nevertheless, while blockade of the dopamine receptor is an obvious explanation of the extrapyramidal actions of neuroleptic drugs, some controversy exists about the extension of that mechanism to explain their antipsychotic effect. The principal argument to the contrary (Crow & Gillbe 1974) is that the correlation between extrapyramidal and therapeutic effects is not perfect. Some drugs (such as thioridazine) have fewer Parkinsonian effects than would be expected from their clinical efficacy. These same drugs, however, have high anticholinergic potency (Miller & Hiley 1974)—in other words, they have "inbuilt" anti-parkinsonian activity. When this is taken into account, the relation between dopamine antagonism and therapeutic effectiveness becomes more compelling. In the corpus striatum, where there is an interaction between acetylcholine and dopamine, drugs with a low incidence of side effects have relatively weak effects on dopaminergic transmission. This interaction may not occur in the mesolimbic dopamine system (the nucleus accumbens and related structures), and here dopamine blockade correlates better with therapeutic effectiveness (Anden 1972; Crow et al. 1977). Moreover, when dopamine antagonism is assessed not in the adenylate cyclase

[1]Division of Psychiatry, Clinical Research Centre, Harrow, England HA1 3UJ.

system but as inhibition of butyrophenone binding (as assay that probably identifies a second type of dopamine receptor) the relative lack of potency of the butyrophenones disappears (Creese et al. 1976; Seeman et al. 1976). A recent clinical study (Johnstone et al. 1978a) showed that only the cis- or α-isomer of the thiaxanthene flupenthixol, which blocks the dopamine receptor, is effective in treatment; the β-isomer, which is very much less potent as a dopamine antagonist, is no more active than placebo. This result is hard to explain except on the basis that dopamine antagonism is necessary for the therapeutic effects. The dopamine blockade theory of neuroleptic action has thus survived stringent tests; and antagonism of dopamine receptors, particularly those located within the mesolimbic system and the subset that is specifically labeled by butyrophenones, is most probably the critical element in diminishing schizophrenic symptoms.

Amine Theories

Is there, therefore, a primary disturbance of dopaminergic transmission in schizophrenia? Probenecid blocks the elimination of the dopamine metabolite homovanillic acid (HVA) from cerebrospinal fluid and can be used to obtain an estimate of dopamine turnover in the central nervous system. Use of this technique (Bowers 1974; Post et al. 1975) has produced no evidence of an increase in HVA that could be attributed to overactivity of dopamine neurons. Indeed, within the group of schizophrenic patients poor prognosis (Bowers 1974) and increasing severity of symptoms (Post et al. 1975) are associated with decreased concentrations of HVA in the cerebrospinal fluid. Postmortem studies (Owen et al. 1978) have also shown no evidence of increased dopamine turnover—a surprising finding, since many patients coming to necropsy have been on long-term medication. Presumably, as in animal experiments, the acute effects of neuroleptic drugs on dopamine turnover disappear with continued administration. These studies give no support to the view that dopamine neurons are overactive in schizophrenia.

By contrast, there is evidence (Owen et al. 1978; Lee et al. 1978) that the number of dopamine receptors is increased in the brains of a proportion (perhaps two-thirds) of patients with schizophrenia, as shown by receptor assay techniques. In experiments on animals, the number of receptors has been found to increase after administration of neuroleptics; but the size of the change (around 100%) in schizophrenic patients is relatively large, and there is an increase in some patients who had been free of medication for the year before death (Owen et al. 1978). Moreover, two types of dopamine receptor can be identified by ligand-binding techniques, and only that type of receptor labeled by the butyrophenone antagonist drugs is increased in schizophrenia (Owen et al. 1980; Cross et al. 1981), while receptors labeled by both antagonist and agonist compounds are increased after administration of neuroleptics (Muller & Seeman 1977).

Other neurohumoral theories have been tested in postmortem studies of the brains of schizophrenics. On the basis of the LSD psychosis and the pharmacological antagonism by LSD of some effects of serotonin, Gaddum (1954) suggested that serotonergic transmission might be deficient. Tryptophan metabolism (by way of the serotonin and other pathways), however, is not abnormal in the schizophrenic brain (Joseph et al. 1979), and serotonin receptors (assessed by binding of LSD and 5-hydroxytryptamine) are unchanged (Owen et al. 1980; Whitaker et al. 1981). There have been conflicting reports on possible changes in monoamine oxidase activity in platelets (Murphy & Wyatt, 1972) in schizophrenia, but interest in the question has been diminished by the finding (Crow et al. 1979a; 1981) that enzyme activity, assessed with several different substrates, is normal in the brains of schizophrenics. Finally, there is evidence (Crow et al. 1972) that certain noradrenergic pathways (such as the locus coeruleus innervation of the cerebral cortex) play a part in reward mechanisms; Stein and Wise (1971) suggested that these pathways degenerate in schizophrenia. A deficient response to rewarding stimuli is a plausible explanation for some features of the disease, but studies (Cross et al. 1978) of the enzyme dopamine-β-hydroxylase (a marker for noradrenergic neurons) have not shown a consistent reduction in the schizophrenic brain.

At present, therefore, the only change found consistently in the postmortem studies of the schizophrenic brain is an increase in the numbers

Table 1

Neurohumoural Hypotheses of Schizophrenia

Authors	Theory	Principal Arguments	Evidence from Postmortem Studies	
			For	Against
Gaddum 1954; Woolley and Shaw 1954	Serotonin deficiency	LSD psychosis resembles schizophrenia, LSD blocks serotonin receptors		Serotonin turnover not decreased (Joseph et al. 1979) Serotonin receptors unchanged (Owen et al. 1980; Whitaker et al. 1981)
Randrup and Munkvad 1965, 1967, 1972	Dopamine neurone overactivity	Amphetamine psychosis resembles acute paranoid schizophrenia. Amphetamines increase dopamine release. Antipsychotic drugs block dopamine receptors		Dopamine turnover not increased (Owen et al. 1978)
Bowers 1974; Crow et al. 1976	Dopamine receptor supersensitivity	As above	Dopamine receptors increased (Owen et al. 1978; Lee et al. 1978)	
Stein and Wise 1971	Noradrenaline neuron degeneration	Reward processes are mediated by central noradrenergic systems; anhedonia is a core feature of chronic schizophrenia		Dopamine-β-hydroxylase not reduced (Cross et al. 1978)
Murphy and Wyatt 1972	Monoamine oxidase deficiency	Platelet monoamine oxidase activity is reduced in some schizophrenic patients		Monoamine oxidase activity not reduced (Crow et al. 1979a)

of dopamine receptors. If this change is related to the disease process rather than to its treatment, it could explain the beneficial effects of dopamine receptor blockade.

Problems for the Dopamine Hypothesis

However, there are problems for this modification of the dopamine hypothesis.

1. It has long been recognized (e.g., Hughes & Little 1967; Letemendia & Harris 1967) that neuroleptic drugs are of limited value in many chronic patients. Moreover, Kornetsky (1976) found that such patients are sometimes resistant to the psychosis-exacerbating effects of dexamphetamine which are attributed to increased dopamine release.

2. The therapeutic effects of blockade of dopamine receptors, and possibly of neuroleptic drugs in general, are limited to "positive" symptoms (delusions, hallucinations, and thought disorder). Negative symptoms (flattening of affect, poverty of speech, loss of drive) which are more commonly seen in chronic schizophrenia, are much less affected (Johnstone et al. 1978a).

3. The fundamental defect in some chronic schizophrenic illnesses may be quite distinct from that underlying the acute disturbance. Thus, cognitive changes (e.g., disorientation in time) that resemble those seen in the organic states are seen in some institutionalized patients (Crow & Mitchell 1975; Crow & Stevens1978). Further, several radiological studies (Haug 1962; Asano 1967; Johnstone et al. 1976, 1978b; Weinberger et al. 1979) have suggested that there is a group of chronic patients, probably including those with the greatest deterioration, who have structural changes, as reflected by increased ventricular size of the brain.

Table 2

Structural Changes in Schizophrenia—Association with Clinical State

Study	Test	N	Abnormality	Association
Holden et al. 1973	echo-ECG.	65	3rd vent.	Treatment resistance
Johnstone et al. 1976	CT scan	18	lat. vent.	Intellectual impairment (Withers & Hinton) ? negative symptoms
Rieder et al. 1979	CT scan	17	lat. vent.	Intellectual impairment (Halstead-Reitan)
Donnelly et al. 1980	CT scan	15	lat. vent.	Intellectual impairment (Halstead-Reitan)
Golden et al. 1980	CT scan	42	lat. vent.	Intellectual impairment (Luria-Nebraska)
Weinberger et al. 1980a	CT scan	51	lat. vent.	Poor pre-morbid adjustment
Weinberger et al. 1980b	CT scan	20	lat. vent.	Treatment resistance
Gross et al. 1981	CT scan	117	3rd vent.	"Pure defect" state
Andreasen 1981	CT scan	52	lat. vent.	Negative symptoms Impaired sensorium
Takahashi et al. 1981	CT scan	169	3rd vent., lat. vent., cortex	Blunted affect uncooperativeness

Abbreviations: vent = ventricle
lat = lateral

A summary of the main findings of those studies (one echo-encephalographic and nine CT scans) which have related evidence of structural change to clinical features of the disease (Table 2) reveals that such changes are associated with treatment resistance (two studies), intellectual impairment (four studies), and the presence of negative symptoms (three studies). The most commonly reported abnormality is an increase in lateral ventricular area, but it may be, as suggested by Takahashi et al. (1981) that when third ventricular widening is sought, it is found to be a more consistent change.

4. It has recently become recognized that some symptoms (e.g., Schneider's first-rank symptoms) which have often been regarded as particularly characteristic of schizophrenia are relatively ineffective predictors of long-term outcome (Brockington et al. 1978; Bland & Orn 1980). This is significant in that poor outcome was the characteristic by which Kraepelin considered that dementia praecox could be distinguished from manic-depressive psychosis.

Two Syndromes

To account for these findings, it has been proposed that two syndromes can be distinguished in those diseases currently described as schizophrenic and that each may be associated with a specific pathological process (Table 3). The first (the Type I syndrome, approximating "acute schizophrenia," and characterized by the positive symptoms—delusions, hallucinations, and thought disorder) is in some way associated with a change in dopaminergic transmission; the second process (the Type II syndrome, approximating the "defect state," and characterized by the negative symptoms—affective flattening and poverty of speech) is unrelated to dopaminergic transmission but may be associated with intellectual impairment and, perhaps, structural changes in the brain. Type I symptoms are reversible; Type II symptoms, which are more difficult to define, may indicate a component of irreversibility. The former predict a potential response to neuroleptics; the latter are more closely associated with a poor

Table 3

Two Syndromes of Schizophrenia*

	Type I Syndrome	Type II Syndrome
Symptoms	Positive symptoms (delusions, hallucinations, thought disorder)	Negative symptoms (affective flattening, poverty of speech, loss of volition)
Type of illness in which most commonly seen	Acute schizophrenia	Chronic schizophrenia
Potential for response to neuroleptics	Good	Poor
Presence of intellectual impairment	Absent	Sometimes present
Outcome	Reversible	? Irreversible
Pathological process	Disturbance of dopaminergic transmission (? increased dopamine receptors)	Cell loss leading to structural changes in the brain

*Crow, T.J. *Br. Med. J.*,280-86-88, 1970.

long-term outcome.

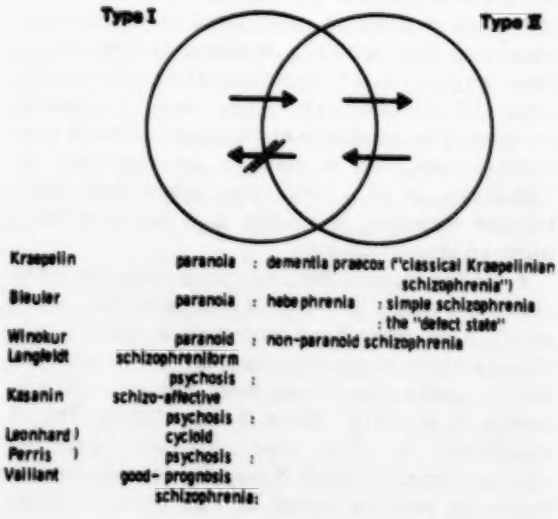
Even if the Type I and Type II syndromes represent different dimensions of pathology, it is apparent that they do not constitute separate diseases.

They are often associated together. For example, episodes of the Type I syndrome (positive symptoms) often progress into the Type II syndrome defect state with or without the persistence of positive symptoms; this might be described as classical Kraepelinian schizophrenia. On the other hand, either syndrome may occur alone. Thus, a pure Type I syndrome which remits may be described as a schizophreniform psychosis (Langfeldt 1960), or "psychogenic" or "reactive" schizophrenia (Faergeman 1963), a cycloid psychosis (Leonhard 1966; Perris 1974), schizo-affective psychosis (Kasanin 1933), or good-prognosis schizophrenia (Vaillant 1964).

The Type II syndrome may occur alone as in simple schizophrenia or in the defect state when positive symptoms have disappeared, and sometimes it may precede the onset of positive symptoms—as in the concept of childhood asociality propounded by Quitkin et al. (1976).

The paranoid/non-paranoid dichotomy can also be related to the concept, paranoid schizophrenia being equivalent to a chronic Type I syndrome, while non-paranoid schizophrenias (including the Bleulerian categories of hebephrenia and simple schizophrenia) are those which include a component of the Type II syndrome. A similar distinction is made by Winokur and Tsuang (1981). The relationship proposed between the two syndromes is indicated in the Figure, together with the correspondence of the three symptom constellations to various nosological terms of current or recent usage.

Of particular interest are the changes which occur with the passage of time. Thus, patients with the Type I syndrome may progress to acquire Type II symptoms, and in due course some of these will lose their positive symptoms. Some may re-acquire them, i.e., experience acute exacerbations of psychosis. What appears to be unusual, and if it does occur is worthy of note, is that patients with negative symptoms (Type II syndrome) should lose these symptoms once they are



FIGURE

established. According to the hypothesis, this is because such symptoms are associated with a structural change in the brain.

The distinction between Type I and Type II syndromes explains a number of findings:

1. Angrist et al. (1980a) found that exacerbation of symptoms in individual patients by amphetamine predicted good response to neuroleptics, while absence of response to amphetamine predicted poor response. Re-analysis of individual Brief Psychiatric Rating Scale (BPRS) symptom scores (Angrist et al. 1980b) revealed that positive symptoms (the Type I syndrome) were exacerbated by amphetamine and improved by neuroleptics, while negative symptoms (the Type II syndrome) showed little change with either drug.

2. In a 30-year followup study, Tsuang (1980) found that disorientation at the time of first psychotic illness is a predictor of poor long-term outcome. Thus, disorientation in the acute illness may be a harbinger of the intellectual impairment of the Type II syndrome.

3. Recently, Owens and Johnstone (1980) have found that negative symptoms in long-stay patients are strongly correlated with intellectual impairment (the Type II syndrome) and also with neurological signs, but that none of these features is significantly related to positive symptoms (the Type I syndrome).

4. The prediction that increased dopamine receptors are related to positive symptoms has been tested in a study of 14 patients whose clinical state had been assessed before death on standardized rating scales. The number of dopamine receptors assessed as maximum spiroperidol binding was found to be significantly ($p < 0.01$) associated with positive but not negative symptoms (Crow et al. 1981).

Causation

The cause of schizophrenic illness remains obscure. A genetic influence is undoubted, but the facts that the onset of symptoms is often in adult life and that concordance in monozygotic twins (about 50%) falls short of 100 percent suggest that genes may be relevant only in predisposing to some other factor. Infection with slow virus may be relevant (Crow et al. 1979b; Crow 1978, 1980, 1981; Tyrell et al. 1979; Albrecht et al. 1980). Some neurotropic viruses (i.e., polio, herpes, simplex and zoster) are selective in the cells that attack. Conceivably a slow virus infection might be associated either with a primary chemical disturbance (i.e., through an affinity for a receptor site), as in the Type I syndrome, or with a more general disturbance of higher cognitive functions associated with structural changes in the brain, as in the Type II syndrome.

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Schizophrenia and Late Maturational Brain Changes in Man[1]

Irwin Feinberg, M.D.[2]

Recent findings in neurobiology suggest that maturational changes take place in the brain much later in life than had previously been thought. In this context, several lines of evidence suggest that a major reorganization of the human brain takes place in adolescence:

1. There is a marked decline in the abundance of deep (Stage 4) sleep and in the amplitude of the delta waves which characterize this stage. Between the ages of 10 and 16 years, these variables show as much change as they do over the next 30 years (Feinberg & Carlson 1968; Feinberg et al. 1977; Williams et al. 1974).

2. A marked diminution in neuroanatomical plasticity occurs. For example, a left hemisphere

[1]This work was supported by the Veterans Administration.
[2]Veterans Administration Medical Center and The University of California at San Francisco 94121.

lesion which causes aphasia in a 10-year-old child is usually followed by full recovery of speech if the right hemisphere is spared; the same lesion in a 20-year-old person results in a permanent aphasia.

3. The ability to carry out sustained logical thinking and to solve complex and abstract problems emerges in full flower toward the end of adolescence. While these skills surely depend upon continued learning, they may also require morphological changes in the neural substrate of thought.

4. The changes listed above are normal developmental phenomena. An abnormal developmental occurrence in adolescence is the emergence of schizophrenia. To be sure, some patients who develop this illness have a long history of behavioral disturbance so that one may question how important a role adolescence itself plays. However, one also finds patients whose psychosocial development was normal or outstanding prior to the onset of a schizophrenic illness. The abrupt change from a social, productive, and happy youngster to a delusional, withdrawn, and frightened schizophrenic is one of the most tragic events in medicine. The profound nature of this change suggests that the neural substrate of behavior has altered in some fundamental way.

Recently, Peter Huttenlocher (1979) of the University of Chicago described a late change in brain morphology which might underlie the striking behavioral and electrophysiological changes of adolescence. He observed a marked reduction in the density of synapses in postmortem specimens of human cortex between ages 2 and 16 years; most of this change seems to take place in late childhood and early adolescence. Huttenlocher's finding (as he himself suggested) could directly account for the reduction in neuroanatomical plasticity which occurs during adolescence. It could also underlie the decline in delta wave amplitude during sleep. The electroencephalogram (EEG) recorded at the scalp is the summation of slow, synchronous potential changes in large neuronal pools; a decrease in connectivity could reduce the size of the neuronal groups capable of synchronous discharge.

The author has commented on the fact that adolescence is characterized by the emergence of the ability to carry out sustained logical operations and solve complex and abstract problems. It might seem counter-intuitive to suggest that a neuronal change contributing to this cognitive development is an actual decline in neuronal connections. But this may well prove to be the case. One plausible model, consistent with Huttenlocher's data, is that shortly after birth all potentially useful interconnections develop. This extremely high density of synapses permits great plasticity but has a cost to information processing: too many neuronal connections may make it difficult to distinguish and organize functionally the particular neuronal chains required for sustained logical thought and problem solving. When, toward the end of adolescence, the connections needed for adaptation have been specified by the organism's interaction with the environment, unexploited connections are eliminated. The effect of this elimination is to reduce neuroanatomical plasticity but to increase certain information-processing capacities.

If synaptic pruning of this sort actually takes place, it would not be the first example of systematic creation and elimination of redundant neural elements in brain development. Programmed cell death (Cowan 1973) plays an important role in regulating the development of the nervous system. In the course of embryologic development, many excess neurons are regularly produced; at later and highly predictable stages, those neurons which have not achieved their appropriate connections die. This mechanism is so highly reproducible that it must be under precise genetic control; so also, one would postulate, is the elimination of redundant synapses much later in development. The mechanisms by which the synapses are eliminated is unknown, but it seems likely that neuroendocrine processes play an important role.

If a widespread, genetically programmed elimination of synapses occurs in adolescence, an error in this process may give rise to schizophrenia. The defect might result from the elimination of too many, too few, or the wrong connections. Elsewhere (Feinberg 1978), it was suggested that corollary discharge mechanisms (Evarts 1971) play an important role in the control of thinking, and that several cardinal symptoms of schizophrenia could be understood as resulting from failure of similar mechanisms in the "motor systems" of thinking.

We have already noted that the extent of neuronal interconnections might determine the size of the neuronal pools whose synchronous,

slow potential change gives rise to delta waves. In this regard, it is of interest that the most firmly established brain abnormality in schizophrenia is a reduction in Stage 4 sleep (Feinberg & Hiatt 1978). This abnormality, although neither specific to, nor invariably present in, schizophrenia, has been found in 40-50 percent of the samples of schizophrenic patients investigated. Computer analysis suggests that it is largely due to reduced delta wave amplitude in the first period of non-REM sleep (Hiatt, Floyd, & Feinberg, submitted for publication).

The highly speculative nature of this discussion is obvious. But whether or not its neuroanatomic basis is the change in synaptic density described by Huttenlocher, there is compelling but as yet neglected evidence that a major reorganization of the brain takes place in adolescence. This reorganization is associated with striking changes in sleep EEG, brain plasticity, and problem-solving capacity. An error in so pervasive a developmental process may be responsible for some types of schizophrenia.

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Dopamine and the Neural Substrates of Depression

Chair: Hans C. Fibiger, Ph.D.
University of British Columbia
Vancouver, B.C., Canada

Evidence In Support of a Role of Dopamine In Affective Illness

Angelos E. Halaris, M.D., Ph.D.[1]

The first indications of a link between dopamine (DA) and affective disorders appeared in the late sixties. It was not until recently, however, that serious consideration was given to DA in addition to other neurotransmitters commonly associated with the pathophysiology of manic-depressive illness. A growing body of evidence suggests that along with norepinephrine (NE) and 5-hydroxytryptamine (5-HT), DA plays a role in affective illness. Newer compounds with selective effects on DA receptors and specific DA agonist or antagonist activity are assisting in the characterization of various subtypes of depression. Correlations between forms of psychopathology and DA metabolism have clearly defined a group of depressives with diminished excretion of homovanillic acid (HVA) in cerebrospinal fluid (CSF). These studies have associated DA with retarded forms of depression and certain aspects of manic behavior.

Compared to the extensive literature on an-

[1]Department of Psychiatry, UCLA School of Medicine, and Veterans Administration Medical Center Brentwood, Los Angeles, CA 90073.

tidepressants and NE or 5-HT, animal studies seeking to establish dopaminergic involvement in antidepressant drug action are relatively sparse. There are two reasons for this disparity. First, DA was long held to be a precursor of NE, lacking any transmitter activity of its own. This assumption later proved to be erroneous. Second, research has focused heavily on NE as the transmitter primarily responsible for the pathogenesis and treatment of affective illness. Thus, the number of basic studies concerned with antidepressant action and dopaminergic transmission is small.

Effect of Tricyclics on DA Metabolism

One of the earlier findings from this laboratory was that chlorimipramine and other tertiary drugs increased DA levels in rat whole brain. The increases were substantial (40-60%) and time-dependent. Since similar time-dependent changes had been obtained with brain levels of 5-HT after chlorimipramine, it was hypothesized that there may be a link between uptake inhibition and changes in amine metabolism, possibly via feedback mechanisms or a direct effect of tricyclics on neuronal firing. This hypothesis led to the detection of DA uptake inhibition by chlorimipramine and other psychotropic compounds. These findings were later confirmed by Ghosh and Hrdina (1977), who obtained marked increases in striatal DA (up to 140%) with imipramine, desmethylimipramine, and amitriptyline. The increase was time-dependent and biphasic. There were concomitant alterations in levels of HVA which were a mirror image of the changes in the concentration of DA. The authors hypothesized that the ability of tricyclic antidepressants to affect striatal concentrations of DA and HVA are relevant to the beneficial effects of these agents in the treatment of Parkinson's disease.

Antidepressant Drugs and Dopamine Uptake

Reuptake blockade of NE and 5-HT by antidepressants and a consequent shift in amine metabolites have been key findings for inferring the therapeutic mode of action of antidepressants and, by extension, the biochemical substrate of affective illness. The possibility that tricyclic antidepressants also inhibit DA uptake had been largely ignored or considered to be of little pharmacological and clinical significance. Using synaptosomal preparations from rat whole brain, it was demonstrated that a number of antidepressants block DA uptake (Halaris et al. 1975; Halaris & Freedman 1975). The degree of inhibition was variable and could not be systematically explained on the basis of molecular structure or side-chain substituents. In the group of antidepressants, it was not possible to detect differences in potency between secondary and tertiary drugs. Among those drugs tested, some secondary (nortriptyline and protriptyline) and some tertiary (chlorimipramine and amitriptyline) tricyclics were potent agents in inhibiting DA uptake. Desipramine, imipramine, and doxepin were weaker, as were iprindole and the tetracyclic maprotiline.

The tricyclic drug concentrations required to produce 50 percent inhibition of DA uptake (IC50 values) were initially considered to be high compared with IC50 values for NE and 5-HT uptake. However, IC50 values obtained in whole rat brain preparations can be misleading, since specific brain regions may exhibit selectivity for inhibition of DA uptake. When regional analysis of DA uptake was performed, the *hypothalamus* was the region in which tricyclic (and nontricyclic) antidepressants produced *in vitro* uptake inhibition in the micromolar range (Table 1). Kinetic analysis revealed that uptake inhibition was of the competitive type. It is noteworthy that iprindole—which has no effect on NE uptake—also inhibited DA uptake in the micromolar range.

In another study, selected tricyclics were injected into rats acutely or chronically. The uptake experiments were performed with synaptosomal preparations from whole brain of pretreated animals. Chlorimipramine, among the most potent antidepressants to inhibit DA uptake, produced significant inhibition, indicating that the drug reaches active sites in spite of the fact that preparations from whole brain rather than hypothalamus were used. Similar results were obtained when lower doses were given for 3 weeks.

Finally, the specificity of the accumulation of labeled amines when performing uptake experiments has often been questioned. It has been

Table 1

Dopamine Uptake in Hypothalamus

Drug	IC_{50} (M)
Desipramine	4.2×10^{-8}
Doxepin	4.4×10^{-8}
Clomipramine	6.3×10^{-8}
Imipramine	7.3×10^{-8}
Bupropion	2.0×10^{-6}
Iprindole	2.2×10^{-6}
Pridefine	2.5×10^{-6}

suggested that biogenic amines can be taken up by nerve-endings other than those of the transmitter used. This is likely to occur at high substrate concentrations. However, if the concentration of labeled amine is less than the Km for the high affinity uptake system, then the risk of nonspecific accumulation is minimized. To rule out that tritiated DA is partially taken up by noradrenergic terminals in hypothalamus, the freely cycling female rat was used as a test model. It was demonstrated that the cyclic and phase-dependent pattern of DA uptake by hypothalamic nerve-endings differs completely from that of NE in the course of a full estrous cycle (Davis et al. 1977, 1978). If tritiated DA were entering NE terminals, the resulting pattern of DA uptake during the various phases of the rat estrous cycle would be similar, if not identical, to that of NE.

Uptake inhibition of DA is not unique to tricyclic antidepressants. A number of newer compounds exhibit significant inhibitory activity. In a comparative study of such new antidepressants, Randrup and Braestrup (1977) investigated the potency of a number of conventional and newer drugs on the inhibition of NE, DA, and 5-HT uptake. Their results indicate that the newer antidepressants butriptyline, mianserin, and trimipramine are about equipotent with maprotiline, iprindole, and the classical tricyclics in inhibiting striatal DA uptake. Interestingly, nomifensine, a clinically efficacious antidepressant (Pecknold et al. 1975) is one of the most potent inhibitors of DA uptake; it is equally potent with benztropine and seven times more potent than cocaine.

The Case of Bupropion (Wellbutrin®)

Bupropion is a phenylethylamine derivative with clinically established antidepressant activity. Its chemical structure differs from that of conventional antidepressants, and the compound does not significantly affect norepinephrine or serotonin. A number of clinical studies have confirmed that bupropion is significantly better than placebo. Bupropion may exert its antidepressant effects via direct or indirect stimulation of DA receptors. To assess whether bupropion is a direct or indirect DA agonist, two types of experiments were performed. First, the effect of bupropion on DA uptake in striatal synaptosomal preparations was determined. Second, use was made of the stereotypy response believed to be mediated by striatal dopaminergic neurons. The uptake experiments revealed bupropion to be a moderately potent inhibitor of striatal DA uptake (Table 2). When injected into rats, it elicited stereotyped behavior in a dose-dependent manner. Since these experiments did not differentiate between a direct vs. indirect DA agonist activity of bupropion, an animal model for surgical induction of DA receptor supersensitivity was devised. This model will be discussed briefly.

By means of parasaggital knife cuts performed bilaterally, the ascending nigrostriatal fibers were transected prior to their entry into the striatum. The lesion resulted in a 96 percent depletion of striatal DA by the fourteenth day after surgery. Bupropion produced intense stereotyped behavior in lesioned animals on Days 3 and 7 after surgery

Table 2

Effect of Bupropion (Wellbutrin®) on Biogenic Amine Uptake

Amine/Region	IC_{50} (μM)
DA - Striatum	1.5
DA - Hypothalamus	2.0
NE - Hypothalamus	2.8
5-HT - Cortex	154.5

at doses that did not induce stereotypy in sham-lesioned controls. Since DA depletion in striatum was not complete 1 week post-lesion, the appearance of intense stereotypy in lesioned animals was probably due to supersensitive DA receptors responding to enhanced dopaminergic transmission caused by reuptake blockade. However, on the fourteenth day post-lesion, when DA depletion was virtually complete, the stereotypy response of the lesioned animals was much weaker. Since presynaptic terminals have undergone degeneration by 14 days after axotomy, the ability of bupropion to elicit stereotyped behavior at this time is probably due to a direct effect on DA receptors. Therefore, it appears that bupropion is a mixed direct/indirect DA receptor agonist.

Bupropion had no significant effects on 5-HT uptake. While an effect of the drug on noradrenergic transmission has not been ruled out, bupropion appears to act primarily via a dopaminergic mechanism. Whether the results from the above animal experiments can explain bupropion's clinical antidepressant efficacy remains to be established.

Behavioral Effects and Conclusions

Two reports have described behavioral effects of tricyclic antidepressants mediated by dopaminergic mechanisms. Molander and Randrup (1976a,b) used gnawing behavior in mice as an index of dopaminergic activity. The antidepressants tested potentiated gnawing induced by levodopa in combination with a decarboxylase inhibitor. In a followup study, these drugs also potentiated the apomorphine-induced gnawing. The authors concluded that tricyclics enhance behaviors associated with brain DA.

Taken together, the above observations give strong support to the contention that tricyclic and non-tricyclic antidepressants affect dopaminergic transmission in the CNS. These drugs exert significant effects on the uptake and metabolism of brain DA and potentiate behavioral effects commonly attributed to dopaminergic mechanisms. However, the relevance of the animal studies to the clinical efficacy of tricyclic antidepressants, the induction of mania in susceptible manic-depressives, and the exacerbation of schizophrenia with these drugs remains to be established. Certainly, the clinical effects of the newer, non-tricyclic antidepressants, such as nomifensine and bupropion, compel attention to DA as a neurotransmitter involved in manic-depressive illness.

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Mania, Depression, and Brain Dopamine: An Overview

Axel Randrup, Ph.D.,[1] Ib Munkvad, M.D.,[1] and Rasmus Fog, M.D.[1]

Dopaminergic mechanisms in the brain seem to be importantly related to the pathogenesis and treatment of several neuropsychiatric diseases, i.e., mania, depression, schizophrenia, Parkinson's disease, and Gilles de la Tourette's disease.

The relation with the affective disorders was suggested in the early 1970s by the following: antimanic, antidepressive, and depressogenic effects of neuroleptic drugs (dopamine blockers); effects of amphetamines, apomorphine, and L-DOPA (dopamine agonists) on mood and affective diseases; correlation of Parkinsonism and other disorders of the basal ganglia with depression; effects of thymoleptics on animal behavior believed to be associated with changes in brain dopamine, etc. (Randrup et al. 1973a, .1973b, 1975). In the years following, this body of evidence was strengthened by new findings: Involvement of dopamine in an interesting monkey model of depression and in reward mechanisms; marked effects on lithium on supersensitive postsynaptic dopamine receptors and on the turnover of dopamine; effects of tricyclic thymoleptics and electrostimulation (both after repeated application) on dopamine receptors; dopaminergic effects of second generation antidepressive drugs, particularly nomifensine, bupropion, and amoxapine) Harrison-Read 1981; Randrup et al. 1979, 1981a; Serra et al. 1980, 1981; present study group).

The dopaminergic effects of chronic thymoleptics seems to be associated with mild excitatory effects on behavior, but these drugs can also be sedative and exert stress-protecting effects somewhat similar to the "neuroleptic indifference." The mechanisms of these effects are yet largely unknown, although there is evidence indicating dopaminergic involvement. But animal experiments are possible here, and this appears to be a particularly interesting area for future research (Pekkarinen, 1970; Garzon & Del Rio 1981).

Amphetamines produce abnormal behavior in animals and humans, which has been studied as a model psychosis. Stereotypy is a prominent feature of the abnormality, and this feature has a particularly strong correlation with brain dopamine. Many types of behavior can become stereotyped, e.g., sniffing, biting, locomotion, aggressive-defensive posture and, in humans, also mental activities such as thinking. Stereotyped thinking can, for example, consist in rumination on one or a few paranoid ideas. Behavioral and mental stereotypies are also common in endogenous psychoses, and the present investigators have pointed out that constant or long-lasting affects (e.g., melancholic mood) might be regarded as an analogy, in the affective area, of stereotyped thinking and behavior (Randrup et al. 1981a, 1981b).

The hypothesis that brain dopamine is importantly related to mood and affective disorders has been strengthened by recent evidence, but it has also become increasingly clear that the relation is not a simple one, and more is known now about the interaction of dopaminergic and non-dopaminergic systems in the brain.

[1]St. Hans Mental Hospital, Dept. E., DK-4000 Roskilde, Denmark.

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Nonlinear Dynamics in Brain Processes

Chair: Arnold J. Mandell, M.D.
Department of Psychiatry
University of California
La Jolla, California

A Mathematical Model for the Effect of Tetrahydrobiopterin Level on Tyrosine Hydroxylase Kinetic Fluctuations[1]

Patrick V. Russo, B.S.[2]

For twelve years Mandell's group, among others, has been studying the regulation of brain tyrosine hydroxylase and tryptophan hydroxylase and using in traditional kinetics experiments the saturating conditions prescribed by the Michaelis-Menten approach (Mandell 1978). However, during the last several years it has become clear that physiological concentrations of the substrates tyrosine and tryptophan and their cofactor tetrahydrobiopterin (BH_4) in brain are well below saturation; they are, in fact, below their K_m for their respective enzymes (Friedman et al. 1972; Wurtman et al. 1974; Bullard et al. 1978; Mandell et al. 1980; Lovenberg et al. 1982). Therefore, the group has undertaken kinetic experiments in which assay concentrations of co-reactants are brought as near as possible to physiological levels, and the enzyme activities are sampled at fine-grained intervals of observation across time or across increasing reactant concentration.

Figure 1 is a schematic comparison of results obtained with saturating vs. non-saturating substrates. Observe the reiterative multiple velocity plateaus generated by the non-saturating condition for both time courses and substrate kinetics. What at first appeared to be noise was shown eventually to be small but reproducible

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[2]Department of Psychiatry, School of Medicine, University of California at San Diego, La Jolla, CA 92093.

variance which required for its quantification a fresh analytical approach.

Time series analysis was found to be a useful descriptive tool. Time courses and substrate kinetics are detrended by linear regression with subsequent normalization to remove the slope and intercept. The raw data are thus transformed to a zero-mean time series of A values, allowing analysis of both its amplitude and frequency components.

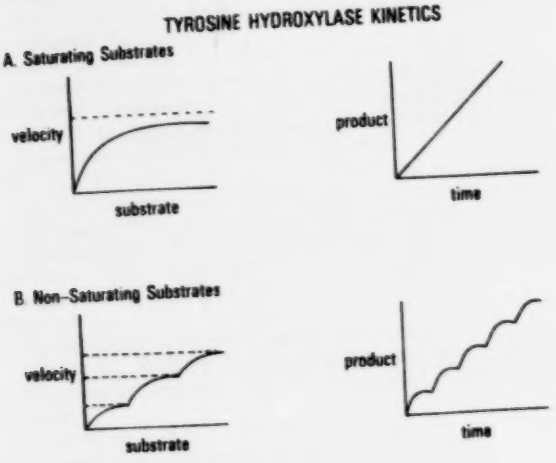


FIGURE 1

One measure of amplitude is root mean square (RMS) of A, defined as $\sqrt{\Sigma A^2/t}$. Squaring the individual values removes the negative ones, so the greater the amplitude or energy of the fluctuations, the higher the average RMS_A. To characterize its frequency or periodic nature, the series is subjected to Fourier analysis, and the resulting power spectrum reveals the relative amounts of power occurring across a range of frequencies. In addition, the Hausdorff-Besicovitch dimension D (Mandelbrot 1977) has provided an index of composite frequency or the dimensionality of the system. These qualitative metrics and their derivation appear in detail in several publications (Knapp et al. 1981, 1982; Knapp & Mandell 1982; Mandell & Russo 1981; Mandell et al. 1982).

In many systems there is a negative correlation between frequency and amplitude, for example, in the electroencephalograph (EEG) where fast waves are typically low voltage and slow waves are generally high voltage. In the present studies a similar relationship exists between D (composite frequency) and RMS (composite amplitude). For control preparations the negative slope appears in plots of D vs. RMS, but certain manipulations such as the introduction of certain pharmacological ligands can uncouple that inverse relationship (Knapp 1982; Knapp et al. 1982; Mandell et al. 1982).

Figure 2 shows the usual D vs. RMS relationship in tyrosine hydroxylase as well as the power spectra as BH_4 is increased. The asterisks represent relative power at various frequencies; the range of frequencies, expressed in the reciprocal as wavelengths, is from 80 minutes on the left to 2 minutes on the right. As BH_4 is increased from 2 to 20 μM, the predominant wavelength moves from 40 to 20 minutes to about 10 minutes, and finally to 4 minutes, with the possible re-emergence of the 40-minute wavelength.

Examination of the effects on these indices of various pharmacological agents (i.e. propranolol, amphetamine) and experimental conditions shows that instead of an unlimited variety of amplitude and frequency profiles, only three or four are possible for the reproducible variance to inscribe. A strong frequency can form, become faster or slower, change in amplitude or dampen, or randomize into a chaotic regime. Several mathematical models were tried in searching for characteristic profiles, and several nonlinear dynamical systems suggested that the profiles could be simulated mathematically (Lorenz 1963; May 1976, 1980; Rössler 1976).

Mathematically, the simplest example is from an equation used in population dynamics and reviewed by May (1980). The limited range of possible profiles is shown in Figure 3. The reiterative equation contains only one parameter, the force term r, which is increased to the values shown in the respective panels with the following results. The system moves from equilibrium at $r = 1$ to a damped oscillator around $r = 2$, to a fast limit cycle around $r = 2.5$. At $r = 3.92$ a slower limit cycle is apparent; at $r = 4.0$ a chaotic regime is seen; finally at $r = 6$ the system is at equilibrium or death. The force term r is reminiscent of changing BH_4 cofactor level in the enzyme assays. At very high levels of BH_4 no fluctuations

TYROSINE HYDROXYLASE PRE–INCUBATION TIME COURSE

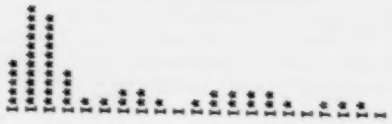
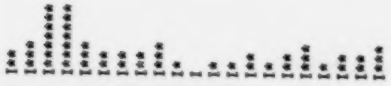
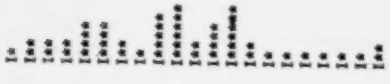
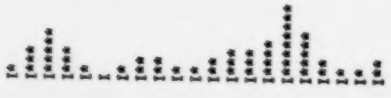
μM BH_4	RMS *A*	D	Power Spectra
5	6.5	1.85	
10	5.2	1.87	
15	4.0	2.05	
20	3.9	2.01	

FIGURE 2

are observed (not unlike the equilibrium "death" at a very high r value, Figure 3). At low or intermediate levels of BH_4 or substrate, long or short wavelengths predominate, with "chaotic" regimes interspersed.

In sum, because endogenous levels of substrate and cofactor in brain as well below saturation, valuable new information may be obtained with subsaturating, more nearly physiological assay constituents, and the subsequent application of appropriate mathematical descriptors of the dynamical character of the resulting data.

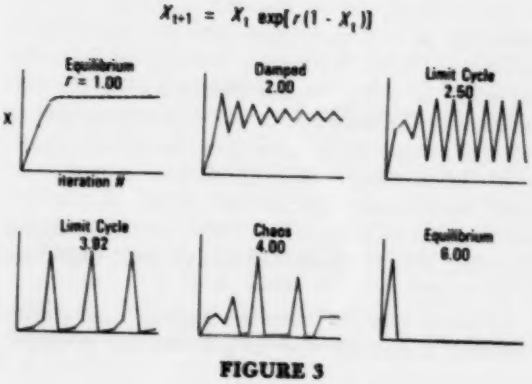


FIGURE 3

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Ordering the Fluctuations of Tryptophan Hydroxylase: Lithium and Chlorimipramine[1]

Suzanne Knapp, Ph.D.[2]

Tryptophan hydroxylase (TPOH; E.C.1.14.16.4) demonstrates stable hyperbolic kinetic functions under equilibrium assay conditions, i.e., when concentrations of substrate (tryptophan) and cofactor (tetrahydrobiopterin, BH_4) are saturating. However, as the concentration ratio of cosubstrates and enzyme approaches unity the system becomes unstable, manifesting kinetic functions with reiterative plateaus across increasing cofactor concentration (Knapp & Mandell 1979). Measures of TPOH activity under non-equilibrium conditions across small increments of cofactor concentration or time have shown velocity fluctuations characterized by multiple saturation plateaus over cofactor and multiple power (frequency) spectral peaks over time, suggesting that the population dynamics of a complex system of dissipative oscillators may be reflected in the enzyme's kinetic processes (Knapp & Mandell 1982; Knapp et al. 1981).

In clinical studies, lithium slows the frequency and reduces the amplitude of the recurring mood cycles characteristic of manic-depressive disease (Schou 1973). Likewise, at the macromolecular level, lithium slows the frequency of Purkinje cell discharge rate (Schultz et al. 1981), of neurotransmitter receptor rhythms in the central nervous system (CNS) (Kafka et al. 1982), and of electroencephalograph (EEG) (Itil & Akpinar 1971), and reduces the amplitude of evoked field potentials of dentate granule cells in rat hippocampal slices (MacVicar et al. 1981). Tricyclic drugs, which share with lithium clincial antidepressant properties, also slow the frequencies of Purkinje cell discharge rates (Schultz et al. 1981) and CNS receptor rhythms (Kafka et al. 1982). This report describes the effects of lithium and the tricyclic antidepressant chlorimipramine (CMI) on the frequency and amplitude components of rat raphé TPOH velocity fluctuations

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[2]Department of Psychiatry, School of Medicine, University of California at San Diego, La Jolla, CA 92093.

observed in both short and long residence time kinetics.

In variational kinetic studies, the fundamental unit of data is the amplitude of deviation (A) of each averaged product concentration point at a given coreactant concentration or time from the mean velocity function as determined by linear regression analysis, normalized for slope and intercept. Computer routines are available from the International Mathematics and Statistics Library with which to perform time series analysis on the A values. The average amplitude or energy of the process is calculated as the root mean square (RMS) of A. The "frequency morphology" of the enzyme population of dissipative oscillators is determined using autocorrelation functions, power spectra, and an independent descriptor, the Hausdorff-Besicovitch dimension D (Mandelbrot 1977), a scale-invariant exponent reflecting the complexity of the perimeter of the one-dimensional A map of the complex function. The rougher the surface of the A function, the more often it changes direction, the longer the perimeter, and the higher the value of D, indicating an increase in degrees of freedom, fluctuation frequency, and the dimensionality of the system. Changes in D of 0.04 to 0.06 are replicable. The analytic methods used are further

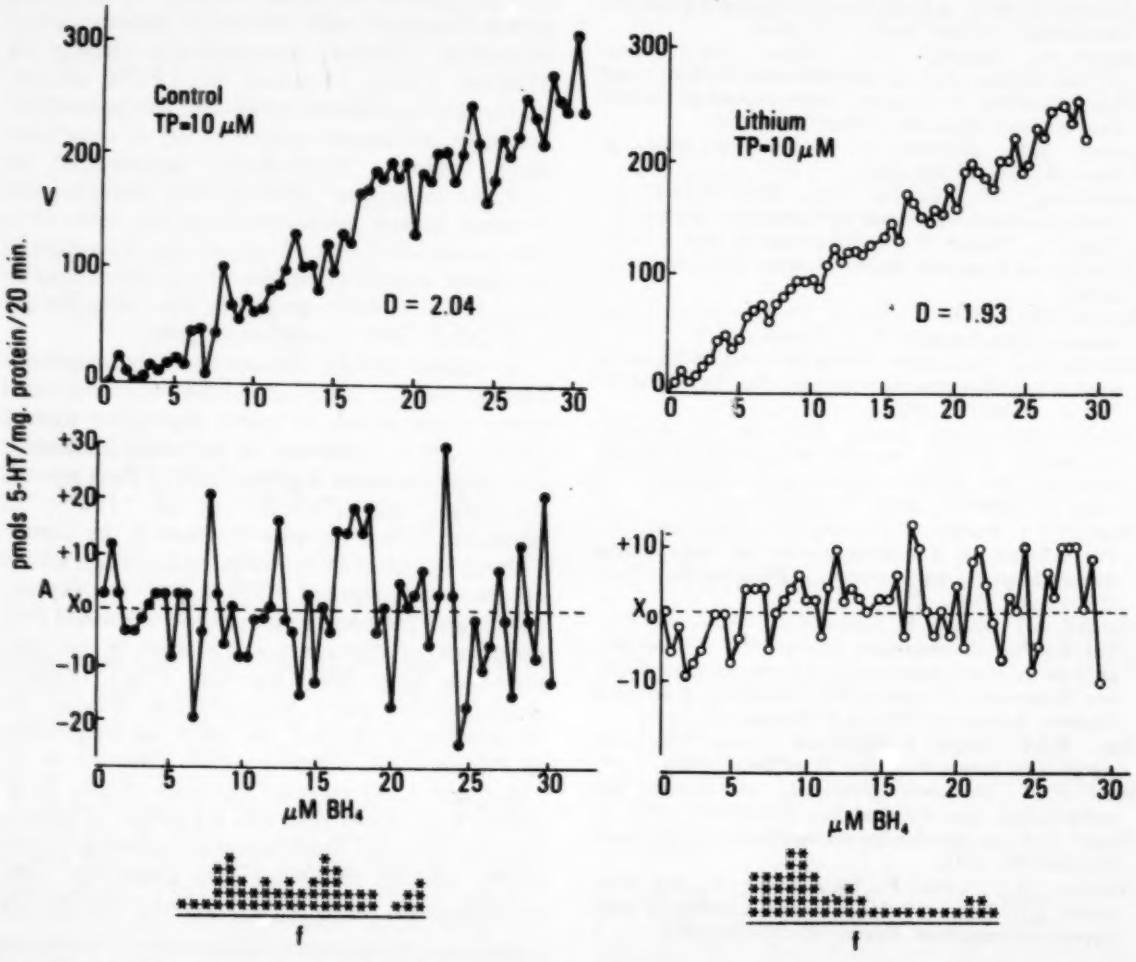

FIGURE 1. Cofactor-velocity functions, A-value transforms, and power (frequency) spectra of TPOH kinetic behavior in the absence and presence of 3 μM lithium.

detailed elsewhere (Mandell & Russo 1981).

Figure 1 presents the results from typical fluctuation experiments in which average product concentrations were determined from 60 duplicate assays across cofactor concentration at intervals of 0.5 μM BH_4. The upper portion of the figure shows the velocity functions obtained in the absence and presence of 3 μM lithium. Below them are shown the A value transforms, which clearly illustrate a lithium-induced reduction in the amplitude of variation. Fourier transformation of the A values from each experiment yielded the power spectra shown, in which the abscissa represents frequency in intervals of cofactor concentration, and the ordinate represents the distribution of power. The diffuse distribution of peaks across the control spectrum suggests multiple subpopulations of phase; in the presence of lithium a single broad peak is observed in the range of increasing cofactor concentrations, consistent with the ion reducing the heterogeneity of the enzyme population. The lower D value also reflects the slower fluctuation frequency in the presence of lithium (1.93 vs. 2.04 for the control sample).

Figure 2 demonstrates the relationship between the average frequency (D_A) and amplitude log (RMS_A) of TPOH when assayed across time in the absence and presence of lithium or CMI. Each point represents the average frequency and amplitude values from one independent experiment; each experiment consisted of 60 duplicate assays performed across time at concentrations of tryptophan and BH_4 that were held near physiological levels, 10 μM and 20 μM, respectively. On the left, the diffuse scatter of points around a negative slope is consistent with the unstable, variably coupled subpopulations postulated for the control population of enzyme oscillators in the absence of a stabilizing ligand. The negative slope reflects the inverse relationship usually observed between frequency and amplitude. The presence of lithium changes that relationship, as is indicated by the positive slope and the relatively tight distribution of points around it (correlation coefficient r = 0.765). CMI

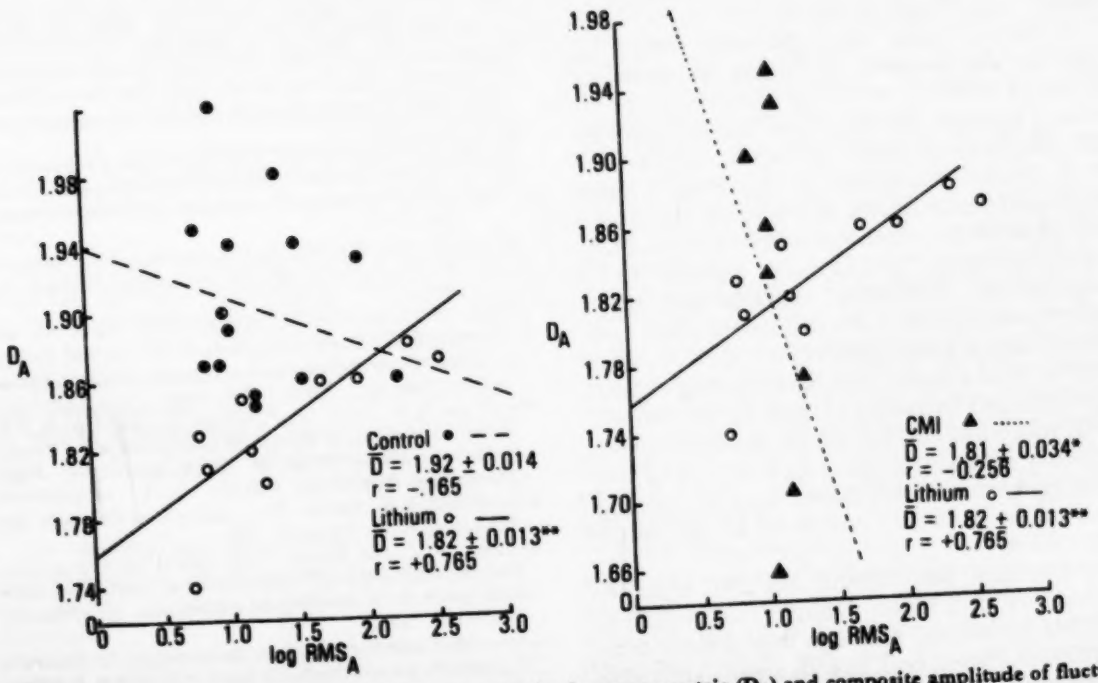

FIGURE 2. Plots showing relationship between composite frequency metric (D_A) and composite amplitude of fluctuations (log RMS_A) in control TPOH preparations and in the presence of lithium or CMI.

also changes the relationship between frequency and amplitude, as is indicated by the almost vertical regression slope. Whereas the ensemble of control points demonstrates a relatively wide range of both average frequencies and average amplitudes, lithium restricts the fluctuation frequency (most D_A values occur between 1.82 and 1.86), but CMI restricts the fluctuation amplitude across a wide range of frequency values. The mean D values, averaged for each group of experiments, indicate that both lithium and CMI significantly slow the fluctuation frequency of TPOH below the control D values of 1.92 ± 0.014.

Alternative to the long residence time TPOH assays across cofactor concentration and time (Figures 1 and 2), short residence time (initial rate) measures were performed in which the enzyme-enriched supernatant containing lithium, CMI, or neither was maintained on ice separate from the assay reactants. At 1.5-minute intervals, duplicate enzyme aliquots were removed and incubated with complete reaction mixtures for 2 minutes, yielding a series of 40 short residence determinations. The Table compares the average D_A values for TPOH activities determined in 25 separate experiments in the absence and presence of lithium or CMI. The significantly higher D_A value in the presence of lithium in these experiments (2.08 ± 0.016 vs. 2.01 ± 0.021 for control) supports the hypothesis that lithium's initial effect is to uncouple the loosely and variable phase control population of nonlinear protein oscillators (demonstrable only with the small temporal observation window of initial rates) and that macromolecular uncoupling results in a Gaussian-like population characterized by a larger number of more like and independent components which phase-gather over time (Winfree 1980) to yield a single population having reduced amplitude and frequency (Figure 2). In contrast, CMI, which had no effect on the mean fluctuation frequency of short residence kinetics, may act by inducing a more homogeneous state of coupling, reducing the variability postulated for the control preparation.

In summary, both lithium and CMI order the fluctuations of TPOH: lithium via frequency, CMI via amplitude. Although they achieve order by different routes, both ligands significantly slow the mean fluctuation frequency of the enzyme activity, altering the inverse relationship usually observed between frequency and amplitude. Short and long residence time studies suggest that different statistical mechanisms of organization of the population of nonlinear enzyme oscillators may underlie the shared and disparate effects of these two classes of drugs.

Table

Estimates of Mean TPOH Product Concentration Frequencies in the Absence and Presence of Lithium or CMI

Condition	N (40-Point Assays)	D_A ± S.E.M.
Control	10	2.01 ± 0.021
Lithium	8	2.08 ± 0.016*
CMI	4	1.99 ± 0.007

*$p < 0.05$ vs. Control; 0.002 vs. CMI

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Characterization of Drug Effects on the EEG by Power Spectral Band Time Series Analysis[1]

Cindy L. Ehlers, Ph.D.,[2] and James W. Havstad, Ph.D.[2]

A method for quantification of the electroencephalogram (EEG) that could be used to characterize drug-influenced states in order to link them to the expression of behavior on one hand, and to underlying biochemical mechanisms on the other, has long been sought. It has been suggested that a language for coherent explanation of specific drug effects at different levels of observation (i.e., from biochemistry to behavior) may lie in the descriptions of drug-induced changes in the distribution of values around mean functions across time or across samples (Mandell 1980).

In the present investigation, the ability of five drugs that are active in the central nervous system to alter the distribution of power in discrete frequency bands of the EEG (a first-order function) was studied. In addition, fluctuations in power in those frequency bands as a function of time, i.e., the power spectral band time series (a second-order function) were evaluated in order to characterize drug effects and correlations to behavior.

The subjects were three adult male Guyanan squirrel monkeys (*Saimiri sciureus*) weighing 835 to 993 grams. Under pentobarbital anesthesia (Nembutal, 35 mg/kg) screw electrodes had been implanted previously in their calvaria in a modified 10-20 array to approximate homotopic locations over frontal and parietal cortices similar to human sites. After at least 2 weeks' recovery from surgery, the monkeys were adapted to a loosely restraining Plexiglas chair for 2 hours, two times a week for 3 months, before the drug studies were begun. The psychoactive compounds studied and their doses were: amphetamine, 0.25 mg/kg; diazepam, 2.5 and 5.0 mg/kg; phenobarbital, 15 and 30 mg/kg; chlorpromazine, 5 and 10 mg/kg; and morphine, 2.5 and 5.0 mg/kg. All were administered orally, by gastric lavage. The order and dose of each drug were randomized for each animal, and at least 5 days elapsed between drug administrations.

On a test day, a monkey is chaired briefly and administered drug or vehicle and then returned to the home cage. Approximately 40 minutes later the animal is returned to the chair and placed in the recording chamber. EEG is recorded for 20 minutes on paper (Grass Model 7D polygraph) and on magnetic tape (Vetter Model D FM recorder) for later computer analysis. The present data were analyzed from artifact-free 15-minute segments of tape from the left fronto-parietal lead (F3-C3). The processing is done by a MINC LS1-11, which digitizes and calculates the power spectra of four-second epochs in 1/4-Hz increments over a range of 0.25 to 64 Hz, a procedure similar to that first described by Joy et al. (1971) and modified by Gehrmann and Killam (1976). The transformed data are then further compressed into eight frequency bands (0.5-1.0 Hz; 1-2 Hz; 2-4 Hz; 4-8 Hz; 16-32 Hz; 32-64 Hz; and 0.5-64 Hz). Mean power density of each frequency band over the entire recording period can then be calculated. In addition, as a function of time, the fluctuations in power density in each frequency band can be displayed as a time series. The calculation of the power spectral band time series is similar to that described by Gehrmann and Killam (1978) and Gehrmann et al. (1977).

The five drugs studied were differentiated from vehicle by various distributions of mean spectral power density in the four bands: 2-4 Hz; 4-8 Hz; 8-16 Hz; and 16-32 Hz (Figure 1). In the lower frequencies (2-4 and 4-8 Hz) amphetamine caused a small increase in power, whereas diazepam caused a dose-dependent decrease.

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[2]Arthur V. Davis Center for Behavioral Neurobiology, The Salk Institute, San Diego, CA 92138.

Phenobarbital had little effect on power density in the lower frequencies. However, both morphine and chlorpromazine caused dose-dependent increases.

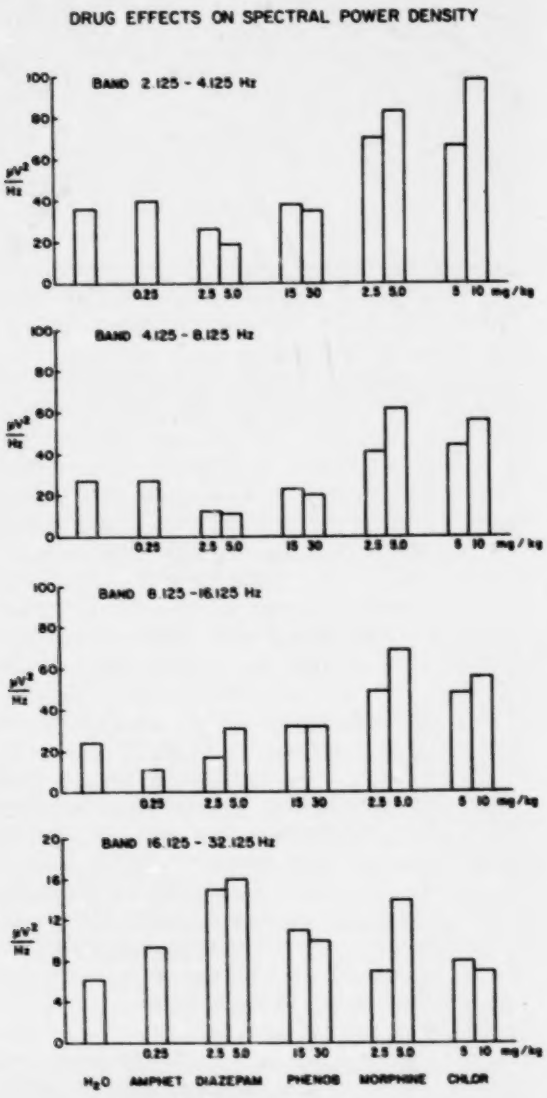

FIGURE 1. EEG mean spectral power density, $\mu V^2/Hz$, in four different frequency bands (2.125-4.125 Hz; 4.125-8.125 Hz; 8.125-16.125 Hz; 16.125-32.125 Hz) recorded from F3-C3 for 15 min in a typical monkey after oral administration of: water; amphetamine, 0.25 mg/kg; diazepam, 2.5 and 5.0 mg/kg; phenobarbital, 15 and 30 mg/kg; chlorpromazine, 5 and 10 mg/kg; and morphine, 2.5 and 5.0 mg/kg.

In the higher frequency band (8-16 Hz), which contains the posterior dominant rhythm, amphetamine caused a decrease in power. A decrease in power density following 2.5 mg/kg diazepam was noted, whereas the higher dose (5.0 mg/kg) caused a smaller increase in power in the 8-16 Hz band. A small increase in power, not dose-related, was also seen following administration of phenobarbital. Morphine and chlorpromazine both caused dose-related increases in power density. A different distribution of power was revealed in the high frequency band (16-32 Hz). Amphetamine and phenobarbital induced small increases in this band, whereas diazepam produced a dramatic dose-dependent increase. Neither chlorpromazine nor the low dose of morphine (2.5 mg/kg) caused any change in power density, but the higher morphine dose (5.0 mg/kg) caused an increase.

Analysis by power spectral band time series provided even better discrimination of drug effects which correlated well with the ongoing behavioral state of the animal. The bands that provided the best discrimination were the two representing frequencies of 8-16 Hz and 16-32 Hz. Under baseline conditions following water gavage or gavage of diazepam vehicle, all the monkeys fluctuated between a "vigilant" state associated with mild motor movement and visual scanning and a quiescent state associated with little visual scanning. This fluctuation in behavioral state was associated with distinct oscillations in the power spectra. During the more vigilant state the EEG was relatively desynchronized, concomitant with an increase in power density in the 16-32 Hz band. When an animal's behavior was quiescent, the EEG was relatively more synchronized, and power increased in the 8-16 Hz band. The oscillation in power spectral density and behavior was very stable under control conditions and was reproducibly altered by drug treatment.

In Figure 2, a distinct difference in the power spectral band time series is obvious after 2.5 mg/kg diazepam. A decrease in the dominant frequency of oscillation and the appearance of a higher frequency fluctuation are associated with a more quiescent behavioral state. A more random pattern of high and low frequency components is seen after 5.0 mg/kg diazepam and associated with mild sedation. A behavioral state and time

FIGURE 2. Power spectral band time series of lead F3-C3 in a typical monkey. Power density fluctuations in bands 8.125-16.125 and 16.125-32.125 Hz are presented from EEG recorded after oral administration of: water; diazepam, 2.5 and 5.0 mg/kg; and phenobarbital, 15 and 30 mg/kg. For each time series, power density ($\mu V^2/Hz$) is represented on the ordinate, and time (minutes) is represented on the abscissa.

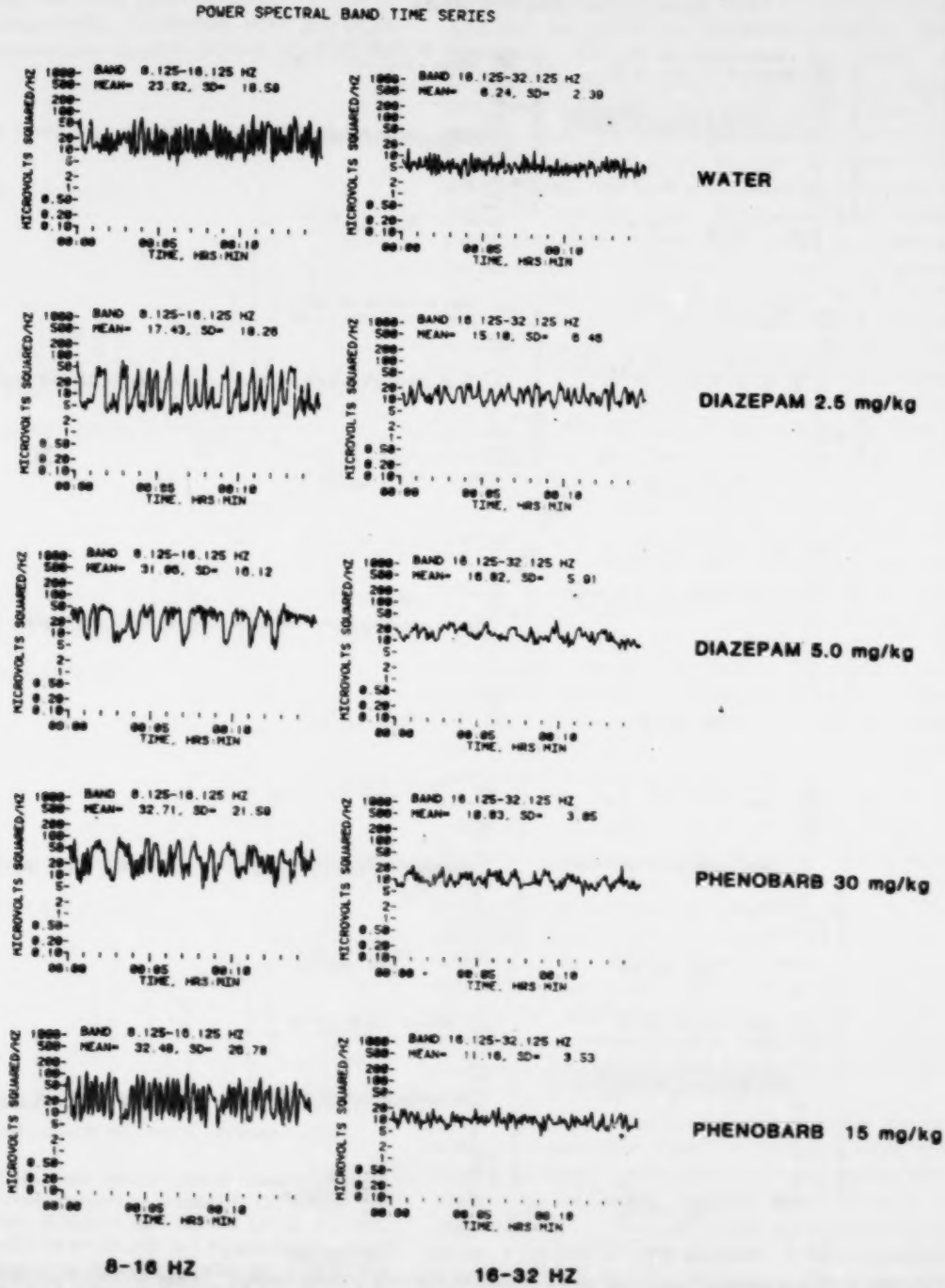

FIGURE 3. Power spectral band time series of lead F3-C3 in a typical monkey from EEG recorder after oral administration of: water; phenobarbital, 30 mg/kg; chlorpromazine, 10 mg/kg; amphetamine, 0.25 mg/kg; and morphine, 5.0 mg/kg. Coordinates are the same as in Figure 2.

series pattern similar to those seen after 5.0 mg/kg diazepam are associated with 30 mg/kg phenobarbital. Although the mean spectral power densities after the two doses of phenobarbital were identical, time series analysis reveals a different pattern of fluctuation after the lower dose, concomitant with very little behavioral sedation. Time series analysis also differentiated the mild sedation following chlorpromazine from that produced by phenobarbital. The increase in mean power spectral density in the 8-16 Hz range from chlorpromazine produced a stable time series that contrasted to the less stable, more random signal after phenobarbital (Figure 3). A stable time series associated with a decrease in mean power in the 8-16 Hz band was seen after administration of amphetamine and was associated with a vigilant behavioral state consisting of decreased motor movement and increased visual scanning, whereas the stability in the time series after chlorpromazine was associated with a state of decreased motor movement and decreased visual scanning. Although the profiles of mean power density with chlorpromazine and morphine were similar (Figure 1), the two drugs were clearly differentiable in the spectral band time series. Whereas the increase in mean power in the 8-16 Hz band after the first was associated with a stable time series, the increase in mean power following morphine was associated with an increase in the amplitude of the dominant rhythm in the time series.

Differentiable profiles in mean power density (a first-order function) in the frequency bands between 2 and 32 Hz after administration of a number of psychoactive drugs in the squirrel monkey are similar to earlier data from Rhesus monkeys (Gehrmann & Killam 1976) and from humans (Fink 1968, 1978; Itil 1974). A clearer differentiation between drugs, and one that relates well to ongoing behavior, can be achieved with power spectral band time series (a second-order function). Gehrmann and Killam (1978) and Gehrmann et al. (1977) previously reported that the benzodiazepines could be differentiated from other sedatives by spectral band time series analysis. The present report expands those observations and further suggests that the spectral band time series may be used to characterize drug-influenced behavioral states. Prigogine and Nicolis (1973) have suggested that the stability of a system is reflected in its second-order fluctuations. Using those principles, Mandell (1981) hypothesized that drug preference might be an effort to stabilize a person's "periodic order" (e.g., amphetamine) or to shift the statistical properties of one's system to a more random, less reactive state (e.g., diazepam, phenobarbital). Further studies may provide evidence to suggest that the EEG can provide an electrographic marker of such cognitive processes.

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Variational and Probabilistic Aspects of Exploratory Behavior in Space: Four Stimulant Styles

Mark A. Geyer, Ph.D.[1]

One of the primary goals of the science of Psychopharmacology is to understand and predict the effects of drugs on the molar behavior of the organism. In animal research, one of the most common behaviors of interest is spontaneous locomotor activity. This presentation describes an unusually detailed approach to the characterization of drug effects on the behavioral activity of rats in a novel environment.

While most activity measures assess only the quantity of activity—that is, activity goes up, goes down, or stays the same in response to a drug—the approach illustrated here provides both graphic and quantitative descriptions of *qualitative* differences in the locomotor activation elicited by stimulant drugs. Qualitative differences in the effects of drugs on activity are readily apparent by observation; but they may be assessed more precisely by examining variability in both the spatial and temporal domains. To illustrate the utility of measures of spatial variability, this report compares the effects of several drugs which, according to measures of the quantity of behavioral activity, are considered to be "stimulants."

Method

Male Sprague-Dawley rats (300-325 gms) were injected intraperitoneally (1 ml/kg) with either saline or the appropriate dose of one of the test drugs, as listed in the Table, 10 minutes before being placed in one of four holeboard/activity chambers for a 1-hour test session. The chamber, diagrammed in Figure 1, is a 12 X 2 inch black Plexiglas box with three floor holes and seven wall holes which serve as specific stimuli for the animal to investigate. As detailed elsewhere (Flicker & Geyer 1982), a Cartesian coordinate system of infrared beams is used to detect the position of the animal within the chamber. Each hole is also equipped with an infrared beam to detect holepokes, and a touchplate on the wall 5 inches above the floor is used to detect rearings. A microcomputer samples these circuits 10 times per second and permanently records all changes. Thus, the exact sequence of locomotor movements, holepokes, and rearings can be reproduced by the computer with a resolution of a tenth of a second in time and an inch and a half in space. The amount of activity can then be calculated as the total number of photobeam interruptions, as is done with several common activity monitors, or as crossovers from one 6-inch sector to another (Figure 1) Crossovers also measure locomotor activity.

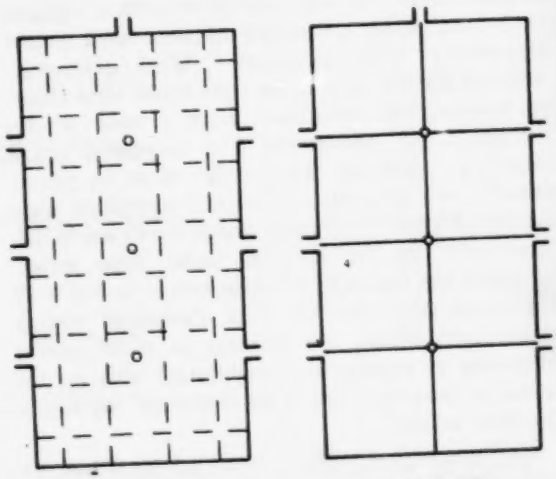

FIGURE 1. Diagram of the holeboard box showing the ten holes in the walls and floor. (A) Dashed lines represent the 8 X 4 perpendicular array of photobeams. (B) Sectors divide the holeboard into eight 6-inch square areas. Crossovers were defined as the number of sector entries and were used as a measure of the amount of locomotor activity.

Standard Measures

The Table summarizes the basic results as hourly means for deltas (total number of photobeam breaks), crossovers, rearings, and both varied and repeated holepokes for the stimulant drugs tested. At the doses used, the various stimulants produced comparable in-

[1]Department of Psychiatry, School of Medicine, University of California at San Diego, La Jolla, CA 92093.

creases in the amount of locomotor activity, as reflected by the deltas and crossovers. Indeed, if these were the only measures examined, one might conclude that these drugs produce similar effects. However, even the simplest of multivariate analyses quickly dispels that notion. In contrast to the other drugs, apomorphine is unusual in that the hyperactivity it produces is accompanied by a decrease rather than an increase in both rearing and holepoking. Furthermore, amphetamine differs from the other drugs in its preferential increase in repeated holepokes into the same hole. Makanjuola et al. (1977) have referred to repeated holepokes as stereotyped as opposed to exploratory holepokes, and have also found them to be preferentially increased by amphetamine.

Table

	Deltas	Crossovers	Rearings	Holepokes Repeated	Holepokes Varied
Saline 1 ml/kg	1802	1289	72	44	39
Amphetamine 1 mg/kg	4708	956	138	144	95
Caffeine 6 mg/kg	4428	776	153	101	123
Apomorphine 1 mg/kg	3974	921	28	11	20
Scopolamine 1 mg/kg	4237	1001	161	54	117

1. DELTAS is the sum of all photobeam interruptions.
2. CROSSOVERS are defined as movements from one 64inch square sector to another.
3. HOLEPOKES were divided depending on whether or not there had been an intervening rearing or poke into a different hole between two pokes into the same hole.

Spatial Patterns of Locomotion

In order to characterize the effects of the stimulants on the patterns of locomotion, one must first understand some aspects of the spatial structure of the locomotor behavior of control animals exploring a novel chamber. When the computer reconstructions of each animal's locomotor patterns are displayed on a video terminal at ten times normal speed, it is evident that each control animal is remarkably consistent in terms of the patterns of locomotion across time and that each animal exhibits a preference for one end or corner, referred to as the home area. The behavior is generally organized as excursions from the home area in which the outward path is typically more varied than the rapid and direct return path.

At the relatively low dose of 1.0 mg/kg amphetamine sulfate, the normal pattern of locomotion is disrupted. The animals rarely exhibit a home area preference and make many seemingly random changes of direction. As demonstrated by Lat (1965) and Schiorring (1979), higher doses of amphetamine produce highly stereotyped, repetitive patterns of ambulation. In contrast, a comparable dose of caffeine produces hyperactivity without altering the normal structure. Caffeine-treated rats consistently exhibit a preference for one end of the chamber, and their behavior is constructed of excursions from this end along reasonably predictable paths. Thus, hyperactivity per se need not disrupt the typical spatial structure of exploratory locomotion. Both apomorphine and scopolamine produce dramatic alterations in the locomotor patterns. Many animals treated with apomorphine persistently and rapidly circle the chamber in a consistent direction for at least 40 minutes, without rearing or investigating the holes. While other apomorphine-treated rats do not rotate, each still exhibits an individualized perseverative pattern that is maintained for an extended period. Scopolamine-treated animals also rotate around the perimeter of the chamber, rarely entering the center. However, virtually all animals given scopolamine rotate one direction several times and then reverse their direction. This characteristic pattern is maintained throughout the session, with the frequency of reversals in direction decreasing with time. Unlike apomorphine, scopolamine-treated animals frequently pause enroute to rear and/or investigate the holes in the wall.

For a variety of reasons, it was important to develop descriptive statistics with which to summarize and quantify these stylistic differences in the effects of drugs on the patterns of locomotion. To condense the data, the chamber is divided into five regions: the two ends; the center; and the two long walls. The number of each of the 16 possible transitions from one region to another is then cumulated and displayed in a two-step transition matrix as if for a Markov Chain analysis. The

coefficient of variation (CV) of this set of 16 values is then calculated as an indicator of the degree to which each animal's locomotor behavior is stereotyped or perseverative in the spatial domain. For example, if an animal's locomotion were uniformly distributed about the chamber, all the numbers in the matrix would be similar and the CV would be small. Conversely, if an animal predominantly repeats the same transitions—that is, he exhibits a stereotyped pattern—the CV would be correspondingly high. Figure 2 displays 40-minute plots of the locomotor patterns of three untreated rats, together with the CVs and the total number of transitions entered into the matrix. It is important to note that, both in Figure 2 and in larger groups of animals, there is no significant correlation between the amount of activity and the degree of its spatial variability.

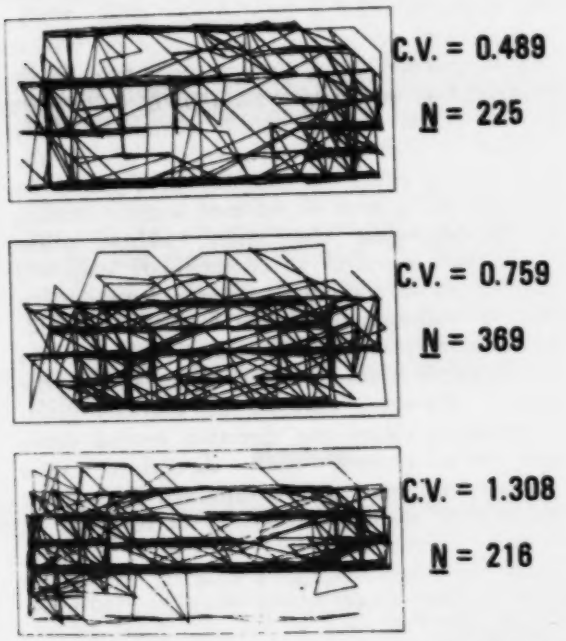

FIGURE 2. Computer reconstructions of the locomotor patterns exhibited by three untreated rats during a 40-minute session are shown together with the Coefficient of Variation (CV) and the number of transitions (*N*), as described in the text.

Figure 3 displays the group means (+/−SEM) for the CVs calculated for the hour of activity following treatment with either saline or one of the stimulant drugs. As suggested in the description of the computer reconstructions of the locomotor patterns, caffeine-treated animals are virtually identical to controls on this measure of variability, while the low dose of amphetamine produced significantly more random patterns. Conversely, both apomorphine and scopolamine significantly increased the CV, reflecting the highly stereotyped locomotor patterns induced by these drugs.

Despite the common characteristic of these stimulants in terms of their effect on the quantity of locomotor activity, each of them produces qualitatively different styles of behavioral activation which can be readily noted by observation and quantified by simple measures of spatial variability. During caffeine-elicited hyperactivity, the normal structure of the locomotor, rearing, and holepoking behaviors are maintained. With low doses of *d*-amphetamine, the spatial pattern of locomotion is randomized and repeated pokes into the same hole predominate. Apomorphine hyperactivity is unique in that rearing and investigatory holepoking are suppressed and the pattern of each animal's locomotion is highly stereotyped. Scopolamine-treated rats also exhibit a stereotyped pattern of locomotion, but one that is clearly distinguishable from that typical of apomorphine. In other studies, it has been

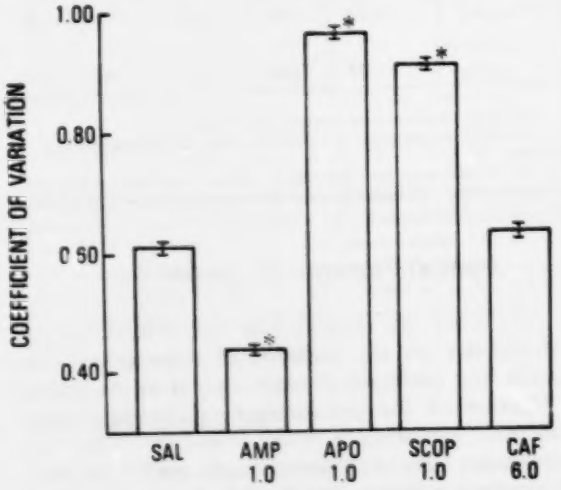

FIGURE 3. Group means (+/−SEM) are shown for the CVs (*see* text) calculated for the entire hour test session. An elevated CV reflects a repetitive spatial pattern of locomotion.

observed that significant changes in the pattern of locomotion can be detected with no change in the amount of activity (Flicker & Geyer 1982).

In the past 10 years, the field of Psychopharmacology has seen remarkable advances in the precision and sophistication of its anatomical, chemical, and physiological measures. It is clear that a similar increase in the sophistication of behavioral assessment techniques is warranted. It is hoped that the methods illustrated in this report will help to meet this need.

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Heart Rate Variational Characteristics in Psychopathology: A Pilot Study[1]

Michael R. Blackburn, Ph.D.[2]

Heart rate variational characteristics in a mixed group of psychiatric patients and the changes in those characteristics accompanying pharmacotherapy were examined. The variational characteristics of heart rate may be described in terms of the magnitude of change (variance) and the temporal pattern of change (periodicity). Variance represents the responsivity or instability in a system and is calculated by taking the average of squared deviations from the mean. Periodicity as used here represents order as detected through time series analyses involving auto correlations over incremented time intervals and their Fourier transformations to the frequency domain (Jenkins & Watts 1968). A relationship may exist between magnitude and the temporal pattern of change characteristic of the system's organization. For example, Zweiner (1978) noted the general positive relationship between period length and amplitude in both heart rate and blood pressure spectra. Because the regulation of heart rate as seen in the dynamics of the interbeat interval (IBI) is, through vagal and sympathetic mediation, normally sensitive to central nervous system events, the variational characteristics of this measure may be a peripheral reflection of central processes in psychopathology. The IBI measure was chosen for study because electrocardiogram recordings are convenient, noninvasive, and generally available.

Two Holter-monitor electrocardiograms (ECG) were obtained on each of 15 psychiatric inpatients of the San Diego Veterans Administration Medical Center. The first was a baseline record taken after 1 drug-free week on the ward. The second followed from 2 to 4 weeks after appropriate pharmacotherapy. Day (between 15:00 and 18:00 hours) and night (between 02:00 and 04:00 hours) ECG samples were transcribed from magnetic to paper tapes using an Avionics electrocardioscanner. Each sample was 24 minutes in length, but was divided into three sequential 8-minute segments for analysis. Thus, each patient was represented by a total of 12 8-minute segments of ECG data. The patient's data were grouped for statistical comparisons on the basis of medication received during therapy. Five patients received the tricyclic antidepressant imipramine; five, the butyrophenone antipsychotic haloperidol; and five, lithium carbonate. Their medical and psychiatric histories were not tabulated until after the ECG data analyses were complete (*see* Table 3). The rationale for grouping patients on the basis of drug assignment was based on the assumption that the clinical psychiatrists provided the most appropriate

[1]The author holds a traineeship from the USPHS under Grant MH-16109.

[2]Department of Psychiatry, School of Medicine, University of California at San Diego, La Jolla, CA 92093.

therapeutic agents for their patients at the time. Furthermore, it was assumed that patients within a group shared factors that differed in degree from patients in other groups and that those factors were related to the reasons they received a particular drug. These expectations are somewhat justified by previous reports of factorial symptom profiles between groups of psychiatric patients receiving different psychotropic drugs (Overall et al. 1972; Overall & Henry 1973).

A time series of heart IBIs was produced from each 8-minute segment by dividing the segment into 40 consecutive 12-second epochs, then the distance between extreme beats of an epoch divided by the number of beats contained within the extremes was used to describe the average IBI for that epoch. A representative IBI was calculated for each of the 40 epochs per 8-minute segment. The means and coefficients of variation of the segment average IBIs were computed and translated to beats per minute. For spectral analysis, the time series were first detrended by least squares linear transformation. The transformed time series were then analyzed by Fast Fourier Transform (FFT) to generate a frequency-power spectrum reflecting the relative amplitude of heart IBI periodicities in frequencies from .04 to .002 Hz (in periods from 24 to 480 seconds, respectively). The spectral peak was identified from the FFT spectrogram as the frequency (period length) with the greatest associated power. Spectral peak power was expressed as a percentage of the total variance of the underlying time series. Results from the spectral analyses of the three 8-minute segments per subject within a condition (for example, baseline day) were averaged to increase within-subject reliability. Analyses of variance were performed on these averaged values. Within-subject correlations of spectral peak period and spectral peak power were computed with the results from analyses of the 8-minute (unaveraged) segments over all conditions (N = 12 per subject). Fisher's Z transformations of the correlation coefficients (Zar 1974) were tested by analysis of variance for group differences. The 5 percent level of statistical significance was tested throughout. All calculations except the analyses of variance were performed on a Burroughs 7800 computer using the International Mathematics and Statistical Library program packages in Fortran.

The three groups differed over all conditions on the measures of heart rate and its coefficient of variation (Table 1A). Heart rate was lower in the haloperidol group than in the other two groups, and the coefficient of variation was lowest in the lithium group. With the groups combined, heart rate was reduced at night, and the spectral peak power decreased at night (Table 1B). The only difference between baseline and drug conditions was a decrease in spectral peak power in the drug condition (Table 1C). Thus, both night and drug therapy conditions were accompanied by reductions in periodicity of heart rate change defined by reduced peak power. There were no interactions between the conditions or between the conditions and the groups. All three groups responded similarly to any change in the condition.

The measures of spectral peak period and spectral peak power were generally correlated in the imipramine and lithium groups, but not in the haloperidol group (Table 2). The positive correlation indicated that there was a linear relationship between period length and the signal-to-noise ratio of the periodicity; that is, when the spectral peak was located at the slow end of the spectrum, it tended to have a higher amplitude relative to the sum of the other variations in the record than a spectral peak located at the fast end of a spectrum derived from other data. In the haloperidol group, periodicity could not be predicted from the location of the period with the greatest amplitude in the spectrum.

Table 1

Average Values of Dependent Measures by Group and Condition

Comparisons		Heart Rate		Spectral Peak	
		Level	Variation[a]	Period Length	Power
A)	Imipramine	84.3 bpm	0.052	195 sec	17.4%
	Haloperidol	71.3*	0.061	199	16.5
	Lithium	84.3	0.035*	182	16.7
B)	Day	89.6	0.050	202	17.9
	Night	70.2*	0.048	169	15.7*
C)	Baseline	79.5	0.054	195	18.1
	Drug	80.4	0.045	175	15.5*

[a]Coefficient of variation of heart rates within subjects
*$p < .05$

Table 2

Within-Subject Correlations of Spectral Peak Period and Power

Imipramine		Haloperidol		Lithium	
Subject	Correlation	Subject	Correlation	Subject	Correlation
1	0.20	1	0.01	1	0.83*
2	0.76*	2	0.28	2	0.78*
3	0.80*	3	0.12	3	0.60*
4	0.62*	4	0.42	4	0.09
5	0.95*	5	−0.14	5	0.28

*$p < .05$

The reduction in spectral peak power with pharmacotherapy is interesting because periodicity has often been associated with pathology (Glass & Mackey 1979). For example, in fetal monitoring during labor and delivery, a sinusoidal heart rate pattern was indicative of fetal distress (Rochard et al. 1976). A similar heart rate pattern was seen in neonatal hypoxia (Reid et al. 1979). Adult obstructive sleep apnea with periodic hypoxia was also accompanied by heart rate periodicity (Tilkian et al. 1977), as are other cardio-respiratory disorders such as Cheyne-Stokes respiration (Dowell et al. 1971) and chronic heart failure (Mantle et al. 1978). Examples of increased periodicity in heart rate were found for psychosomatic disorders (Zweiner 1978) and in oxygen saturation for schizophrenia (Lovett Doust 1980).

In both normal and abnormal cases, heart rate periodicity is usually related to respiration. The respiratory sinus arrhythmia accounts for a large part of the heart rate variation in periods less than 12 seconds in length (Luczak & Laurig 1973; Penaz et al. 1978). The contribution of respiratory sinus arrhythmia was eliminated in the present study by averaging IBIs over 12-second epochs to define each datum point. Sleep apnea could have contributed to the spectral peaks in the 24- to 480-second range, but probably did not because periodicity was reduced at night. Thus the periodicity in this group of psychiatric patients may be unrelated to respiration in the reported range, but reflect disturbances in other central systems. The interpretation of periodicity as abnormal depends, however, on its inappropriateness for the organism's adaptation. Periodicity may be considered pathological to the extent that it reduces the range of potentially adaptive variations. For example, autonomously periodic behavior captured by internal rhythmic mechanisms may become dissociated from environmental events and appear as stereotypy, compulsions, or paranoia. Halberg (1969) suggested that the alteration of periodic processes or the occurrence of periodicity in aperiodic processes may accompany or contribute to disease. If that is so, the restoration of original system variational characteristics may be a requirement for the return to health. This study has not directly demonstrated a change in variational characteristics with disease states, but it has indicated that periodicity may be reduced if the disease signs are ameliorated. Thus the normal condition can be predicted to be one of sensitive instability that allows the organism to respond adaptively to environmental change.

The positive relationship between period length and amplitude is commonly found in many measures, most notably the electroencephalogram, but the haloperidol group is noteworthy here in its failure to develop reliable correlations on these two heart rate variables. The certainty of the uniqueness of the haloperidol patients is reinforced by an examination of the patients' psychiatric classifications in Table 3. Of seven cases with research diagnostic criteria (RDC) indicative of schizophrenia, four were given haloperidol; two received lithium; and one received imipramine. Six of those seven had insignificant correlations of peak period and peak power. Thus the pathology of schizophrenia may involve mechanisms that disrupt the organization of central periodic processes. Neither the average peak location nor the average peak power were different between the haloperidol group and the other two groups. Therefore the distribution of power was no more random within individual spectra, but power did tend to be randomly distributed among the peak frequencies between spectra. This suggests that the haloperidol patients experienced not only periodic central disturbances but that there were inconsistencies in the contributions of these periodic processes. The inconsistency may result in a cognitive and emotional confusion characteristic of schizophrenia. The major psychoses may share the tendency for the central nervous system to become trapped in

Table 3

Characteristics of Sample

Medication Group	Subject	Age	Sex	Race	RDC*	Psychiatric and Medical Notes
Imipramine	1	44	M	W	Major depressive	Pulmonary disease
	2	33	M	W	Major depressive	
	3	46	M	W	Major depressive	Alcoholism
	4	52	M	W	Major depressive	Alcoholism; Bipolar I
	5	23	F	W	Schizoaffective	
Haloperidol	1	38	M	W	Schizoaffective	Bipolar I
	2	25	M	B	Schizoaffective	Alcoholism; cardiac disease
	3	30	M	W	Schizophrenia, paranoid	Alcoholism
	4	52	M	W	Major depressive	Cardiac disease
	5	18	M	B	Schizoaffective	
Lithium	1	57	M	W	Bipolar I	
	2	52	M	W	Bipolar II	Alcoholism
	3	22	M	?	Bipolar II	Records not available
	4	45	M	W	Schizoaffective	Alcoholism; pulmonary disease
	5	25	M	?	Schizophrenia, paranoid	Records not available

*Research Diagnostic Criteria (Spitzer, Endicott, and Robins)

limited modes of function, which modes could differ among the psychoses. Schizophrenia could then be further compounded by an instability between modes, differing from normal in the duration of their fluctuations and consequent inappropriateness to the environment.

Summary

Periodicity of heart rate change in a mixed group of psychiatric patients was found to decrease both at night and subsequent to pharmacotherapy. This finding is consistent with an interpretation of emergent periodicity as a sign of disease and could represent a brain state with limited capacity for adaptation. A subgroup of patients who received haloperidol as part of their indicated treatment during hospitalization was characterized by instability in a function governing rate changes. This instability could represent chaotic central nervous system processes that are manifested in confused cognition and inappropriate affect.

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Attending or Discriminating 40 Hz Modulated Tones Induces Phase-Locked Subharmonic Resonances in EEG

Scott D. Makeig, M.A.,[1] and Robert Galambos, M.D.[2]

Introduction

Recently, Galambos et al. (1981) published a study of brain potentials evoked by trains of tones or clicks at high rates, reporting that the human auditory evoked potential response shows a resonance near 40 Hz. The amplitude of this 40 Hz driven response decreases markedly in sleep. This fact, and the body of experiments linking spontaneous and evoked 40 Hz activity to cognition (Sheer 1970; Spydell 1979), suggested to the authors that the 40 Hz response might be usable to probe level of arousal. What follows is a preliminary report of an experiment designed to explore the effects of attention on the 40 Hz response.

Method

The stimuli consisted of trains of low (800 Hz), middle (1000 Hz), and high (1200 Hz) tonebursts, modulated at 40 Hz, and presented to six subjects under four task conditions — "count the low tones," "count the middle tones," "count the high tones," and "don't count."

The low and high tonebursts were relatively rare (each 12-20% of the total), and the middle tonebursts relatively frequent (60-84%). Four to eight blocks of data were collected from each subject, each block consisting of one run in each of the four conditions. Order of runs within blocks and order of tones within runs were randomized under direct computer control.

Each run lasted about 100 seconds and consisted of 96 tonebursts. Each toneburst consisted of ten tone pips (duration 5 msec), with an interpip interval of 25 msec (onset-to-onset). Each tone pip was composed of four, five, or six half-sinewave clicks. The interval between tonebursts was approximately one second (onset-to-onset), with 200 msec of random jitter introduced in inter-burst intervals to avoid phase-locking to ongoing electroencephalograph (EEG) rhythms.

Subjects were seated with eyes closed in a quiet room. Stimuli were delivered to the right ear at 30 dB above threshold. Subjects reported the task to be difficult, owing to the low level of the signal, the small differences between frequencies, and the necessity of sustaining attention throughout the 2-minute runs. Four channels of evoked responses were collected using Grass EEG amplifiers (bandpass 3-300 Hz) and a Nicolet averaging computer. Results from the bipolar derivation (Cz-Oz) are reported here.

Results

The top two traces of Figure 1 show the averaged (Cz-Oz) responses of one subject to the same

[1]Department of Music, University of California at San Diego, La Jolla, CA 92093.
[2]Children's Hospital and Health Center, San Diego, CA 92123.

FIGURE 1. Average responses to rare targets (top trace), and rare non-targets in the "count high tones" and "count low tones" conditions (middle trace). Bottom trace is the response to the rare tones in the "don't count" condition. Each response is the sum of responses to about 200 tonebursts, in a total of eight blocks of trials over 80 minutes. The thin downward spikes in the responses during the time the toneburst is on are stimulus artifacts. (In these figures Cz positive is upward.)

stimuli (high and low tonebursts in the "count highs" and "count lows" conditions), segregated into "rare target" and "rare nontarget" responses. ("Rare nontargets" are the high tones in the "count lows" condition plus the low tones in the "count highs" condition.) The bottom trace is the responses to these same stimuli in the "don't count" condition (the "rare no counts"). Note in each of these traces the circa 1 μv 40 Hz modulation superimposed on the slower evoked response by the 40 Hz modulation of the toneburst.

The differences between pairs of the three responses shown in Figure 1 are seen in Figure 2. The (target-nontarget) and (nontarget-no count) difference waves each show a regular oscillation at circa 20 Hz which becomes locked in both frequency and phase to the moments of occurrence of tone pips within the toneburst (i.e., to multiples of 25 msec), and continues to at least the end of the sweep (400 msec after onset). A similar 20 Hz characteristic may be seen, less distinctly, in the (target-no count) comparison (Figure 2, bottom trace).

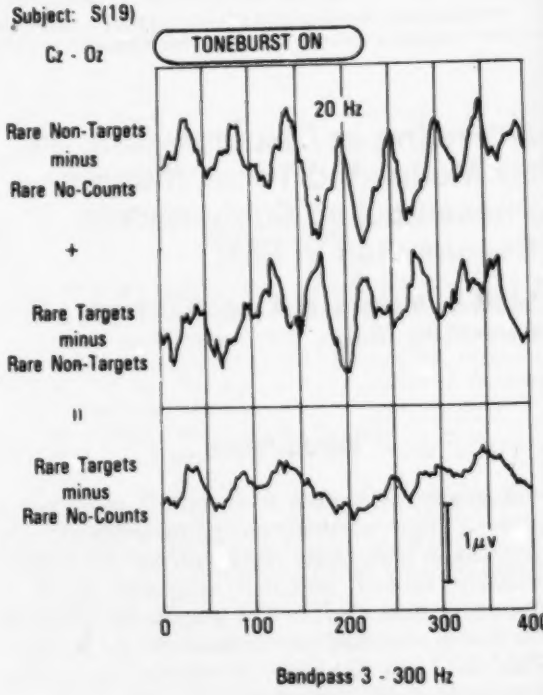

FIGURE 2. Difference waves between pairs of the thr responses shown in Figure 1. Vertical lines are draw every 50 msec. Note the progressive frequency and phas locking of the difference waves and the stability of th phase-locking after offset of the toneburst.

Figure 3 shows the same difference wave comparisons for a second subject. Here frequency-and phase-locked rhythmic difference waves are also evident—but for this subject they are locked predominantly to about 10 Hz.

The (target-nontarget) comparisons for two other subjects are shown in Figure 4. Rhythmicities at about 13 Hz are evident (i.e., at about 1/3 of 40 Hz). In further experiments, evoked rhythmicities at 26 and at 32 Hz (2/3 and 4/5 of 40 Hz) have also been seen. However, rhythms evoked at frequencies other than 10 and 20 Hz have not been seen to "ring" on after toneburst offset, as do difference waves at 10 and 20 Hz (*see* Figure 4).

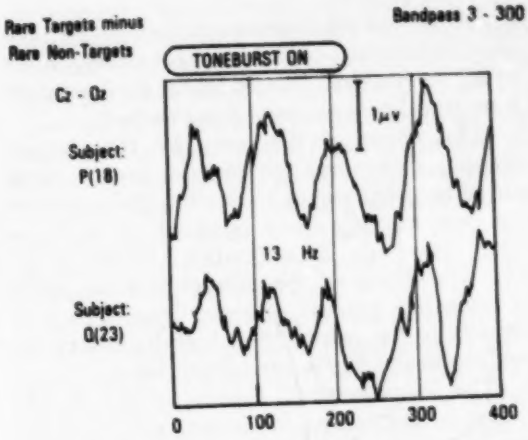

FIGURE 4. The target-nontarget comparisons for two other subjects who show a circa 13 Hz characteristic during the toneburst.

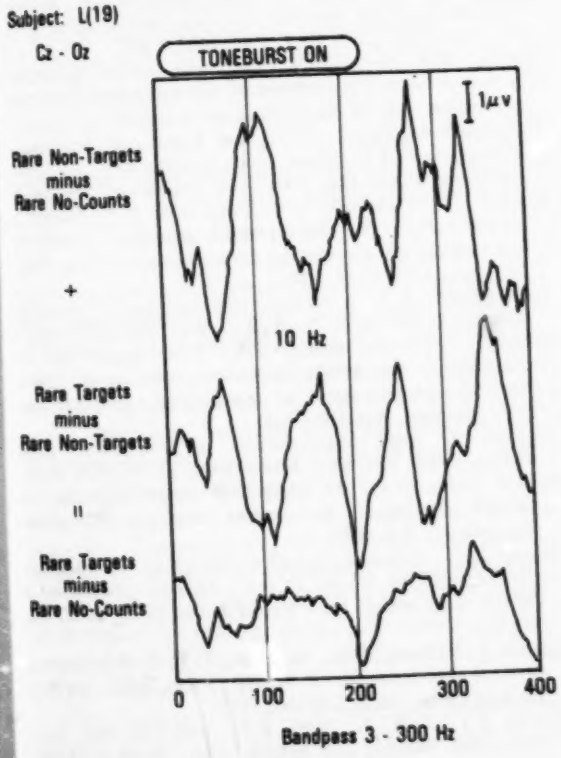

FIGURE 3. The same difference waves as shown in Figure 2 for another subject. Note again the progressive frequency- and phase-locking of the difference waves and their amplitude stability, in this case showing a 10 Hz characteristic.

Tentative Conclusions

Results of these first experiments suggest:

1. Difference waves between responses evoked by target and nontarget 40 Hz-modulated tonebursts reveal differences in amount of nonlinear brain resonance to the modulating frequency of the bursts. These rhythmic difference waves reflect differences in task-relevance of the stimuli, and thus are a new class of endogenous cognitive evoked response, possibly related to the event-related rhythmicities (ERR) discussed by John (*see* Galambos & Hillyard 1981).

2. The rhythmic character of the difference responses seems to be most pronounced in comparisons involving *non*-targets in the "count" conditions. The authors note that similar stimulus-evoked "alpha-like" EEG activity has previously been associated with nontarget stimuli and "inhibitory" cognitive processes (*see* Morrell 1966).

3. The remarkable phase-locking and amplitude stability of the circa 20 and 10 Hz subharmonic difference waves (*see* Figure 2) may be related to the theorized relative stability of successive bifurcations in a variety of physical dynamic systems (Feigenbaum 1979), as well as to bifurcations at these same (40 Hz, 20 Hz, 10 Hz) frequencies reported in various psychophysical (Kristofferson 1980; Augenstein 1955) and electrophysiological (Barnett et al. 1971; Freeman 1961, 1962) experiments.

4. Of the few derivations studied so far, the rhythmic characteristic is seen most clearly in the (Cz-Oz) derivation. This suggests the operation of a central dipole oriented front-to-back.

5. The phase of the circa 10 Hz (target-nontarget) differences corresponds to the same phase of the ongoing alpha rhythm (Oz-positive) which has recently been reported to result in quickest two-flash discrimination (Varelo et al. 1981). The phase of the difference wave could thus indicate a process of central modulation of sensitivity to the intermittent high-frequency information in the 40 Hz modulated bursts.

6. The "after-ringing" portion of the 40 Hz response is augmented for targets and attended tones in some subjects, but not augmented in others.

7. While the degree of stability of these responses within subjects has not been fully assessed, within the sessions reported here these responses seem to be remarkably stable, save perhaps in the "don't count" condition.

Discussion

The authors plan systematic investigations of the range and stability of the responses, and on the effects of changing modulating frequency and modality of the stimuli. They also intend to explore the relation of these phenomena to the endogenous responses (N1, P3, N4, etc.) seen in experiments using unmodulated stimuli (Hillyard et al. 1978).

The present evoked rhythmicities may bear some relation to the harmonic nonlinear phenomena seen in transition to turbulence of driven responses in physical (Feigenbaum 1979; Keolian et al. 1981) and biological (Mandell & Russo 1982) systems. Their range is similar to the variety of harmonic responses to photic driving seen in the raw EEG by Mundy-Castle (1953) and Fukushima (1975). They may also relate to the body of psychophysical theory and experiment relating to "perceptual moments" and "excitability cycles" (reviewed in Harter 1966). While these results are not yet thoroughly tested, they renew interest in exploring the role of nonlinear resonant brain dynamics in cognition.

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Nonlinear Dynamics in Brain Processes[1]

Arnold J. Mandell, M.D.[2]

Universal patterns of behavior, often claimed for human personality syndromes described in the psychoanalytic language of instinct and defense, may be defined and explored more rigorously using global properties of the structure of solutions to N-dimensional nonlinear differential equation sets representative of the behavior of an open, complex interactive system, i.e., the brain. Two conceptual approaches, irreversible thermodynamics and dynamical control theory, make different assumptions concerning the critical determinants of these emergent forms.

Freud lived at 19 Berggasse, "half way up the street" between the homes of the poor below and those of the independently wealthy with higher house numbers (Engelman 1976). The new machines of the Industrial Revolution running on the closed system thermodynamics of Carnot cycles and the Darwinian survival theme of private entrepreneurship were certainly consistent with an energy-dependent psychoanalytic ordering principle of "needs" and their fulfillment. Structure emerged from this dissipation. Energy also drove the fluctuations of the linear, time-dependent diffusivities of Brownian motion (Einstein 1905) that brought an unexpected degree of predictability to randomness for Freud's contemporary Einstein who, working for barely adequate wages at a patent office was, in a way, also "half way up." The need was for survival, and it was attended by a fear of nonlinear unpredictability. Heroic attempts were made to derive N-particle probability densities from functionals of one-particle systems in moderately dense gases—without success.

The dominant turn-of-the-century theme of required energy might explain why the work of two contemporaries of Freud and Einstein, Jung in psychoanalysis, and Poincaré in mathematical physics, was relatively ignored. Jung's message came not from the brainstem but from the upper shakras: myth and form better represented man's supramolecular order that (once fed) organized all the rest (Jung 1956). Poincaré said that given the fact that things were moving already, the constraints (laws) of nature derived not from limitations on activation energy required to get out of a potential well, but restrictive features of interaction; for example, a thing cannot stand on a place that is already occupied. When more than two things are closely engaged, it is difficult to know what comes next with respect to specific predictive parameter values; yet topological dynamics have revealed that there are definite limitations on the number of possibilities (Poincaré 1957). When Boltzmann's dense gas became non-independent particles, even at long times, "slaving" social organization and its measurement via order parameters crept quietly into what is now an exploding physics of complex systems (Haken 1978).

Recent research confirms Kety's findings in the late 1940s that the whole brains of wild psychotic patients and normal sleeping people burn the same mean number of calories per minute (Kety et al. 1948) but are vastly different with respect to the temporal and spatial arrangements of "hot" spots (Sokoloff et al. 1981). A surface on which a multiplicity of topographies can add up to the same mean energy utilization is consistent with the statistical thermodynamics of an ensemble of systems with a variety of entropic "styles" of information transport whose phase relations, couplings, not available fuel, are deterministic with respect to measures of thought, feelings, and action. These ruling dynamical forms appear to lie somewhere between cause and effect.

At the molecular level, a similar isoenergy surface has been portrayed for the multiplicity of hydrogen (proton) configurations on protein macromolecules which determine their electromagnetic moments and therefore their pattern of interactional cooperativity (Kirkwood & Shumaker 1952). Genetic differences in an enzyme can be expressed in altered amino acid sequences away from the active site, leading to no loss of catalytic activity but alterations in the structural stability of the protein associated with

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[2]Department of Psychiatry, School of Medicine, University of California at San Diego, La Jolla, CA 92093.

changes in its regulatory properties and time-dependent patterns of variation in biosynthetic activity (Knapp et al. 1981). These characterizations are not about *what* or *how much*, but about style.

Poincaré's global, geometric, qualitative approach to dynamical systems offers no natural system of coordinates. The portrait of the equation set fills the entire phase space, changing with every turn of the parameter knob; an evolutionary scenario which itself becomes the mathematical object of interest. Surprisingly, qualitative aspects of local, parametized vector space, for example, the stability of the motions of a regional flow near a critical point, may generalize to the entire system (Abraham & Marsden 1967). Psychiatrists knew this already: the obsessional reveals the characteristics of his dynamical brain system in all that he does—from choosing what color socks to wear in the morning to eating each vegetable separately on his dinner plate—all preserving the characteristic symplectic structure of his manifold. The tails of the distribution of values around the mean for any measure reveal a mix of expanding (hysterical) and contracting (obsessional) motions leading to individually unique routes of convergence to invariant measures. Perhaps this reveals the same entropic property seen in statistical physics as characteristic relaxation times or wavelengths of the complex system's spontaneous fluctuations.

Looking through time down the manifold of the mean, attention is paid to the quality of the dynamical activity around it. The Reynolds decomposition of flow separates the average velocity from its varying part. When the graph of a deterministic two-dimensional graph of x causing f(x) is cut transversely, there are distinctive patterns in the surrounding foliage made of what used to be called error. Those in psychiatry are interested in such things: the *hows* that ride on the *whats*, the patterns of variation around the mean, the hetero- and homoclinic orbits that develop around saddle nodes seen in transverse sections, distinctive personality styles that reveal themselves in doing routine things, the process not the content of what goes on in psychotherapy hours.

Quantitative study of these qualities has evolved a variety of useful and closely related abstract metrics: eigenvalue indices of stability; critical exponents describing expansions and contractions of flows; Lyapounov characteristic exponents; geometric and topologic dimensionality; rate of information change; autocorrelation and correlation lengths; probability density distributions, especially the higher moments; phase space topology and geometry; the morphology of transverse sections; and frequency (power) spectra. Symbolic dynamics describe pattern generation and recognition beyond the state space specifics. Those in psychiatry are in search of just such schemes.

The following is a brief example of a characteristic style of evolution by several complex brain systems under repeated perturbation, the transition from a quasi-stable equilibrium to autonomous, limit cycle rhythmicity that might loosely be called a Hopf bifurcation.

Data from a study of single frog muscle end-plate potentials before and after prolonged nerve stimulation (del Castillo & Katz 1954) were digitized and the values expressed as deviations from the mean voltage level (Figure 1). Spectral analysis of the frequency of variation around the mean in these intracellular recordings of random activity shows that the unimodal population, manifesting a single prominent spectral density (top graph and spectrum), split into two subpopulations with the development of response inhibition (bottom graph and spectrum). See Mandell and Russo (1981) for the statistical methods used.

The local anesthetic quinacrine which, like prolonged nerve stimulation or contact with cholinergic agonists, induces a desensitized state [as procaine does Marty (1978)] also binds cholinergic receptors and emits fluorescent noise. Analysis of these receptor fluctuations from the data of Grünhagen and Changeux (1976) reveals a similar dynamical progression (Figure 2). The control at a low drug level shows a single statistical (not limit cycle) spectral peak and associated autocorrelation length. As the system lost its response to the cholinergic agonist—an increase in sodium conductance by a *Torpedo marmorata* electric organ microsac—the spectrum reflected a change from equilibrium behavior to rhythmic "bursting" of a subpopulation observable in the undamped periodicity of the graph of the autocorrelation function. Figures 1 and 2 demonstrate the similarity in statistical manifesta-

tions of desensitization in membrane-conductance and receptor motional processes: the birth from a single population in an (average) equilibrium state of a subpopulation in a limit cycle associated with habituation of the response. After bifurcation there is fast, spontaneous rhythmic activity in a coherent subpopulation, a speculation confirmed by a recent report of the "burst" kinetics of desensitized cholinergic membrane preparations (Sakmann et al. 1980).

At the next level of neurobiological complexity, polysynaptic spinal cord flexor reflexes, an examination of the distributions of interspike intervals in spinal cord interneurons during response habituation, from the work of Groves and Thompson (1973), shows that the interneurons that were capable of a progression from sensitization to an inhibited response after repeated stimulation manifested an initial single population distribution (Figure 3, S), but those that only habituated (Figure 3, H) manifested a multiplicity of frequency-labeled populations (or the phase-locked spontaneous activity of a subharmonically bifurcating chaotic attractor).

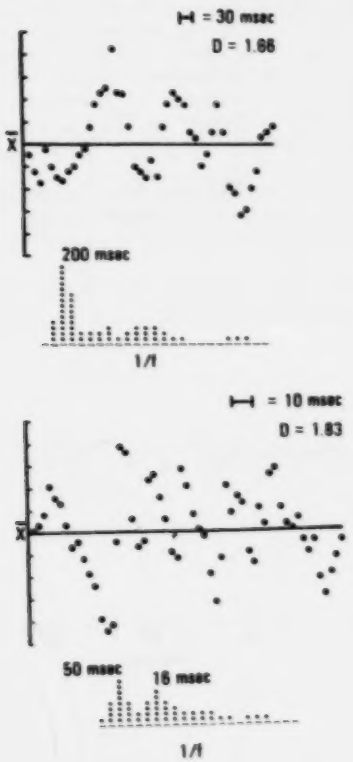

FIGURE 1. Spectral analysis of frequency of variation around mean intracellular recording of "random" endplate potentials before and after prolonged nerve stimulation, showing population bifurcation associated with response inhibition. *See* text.

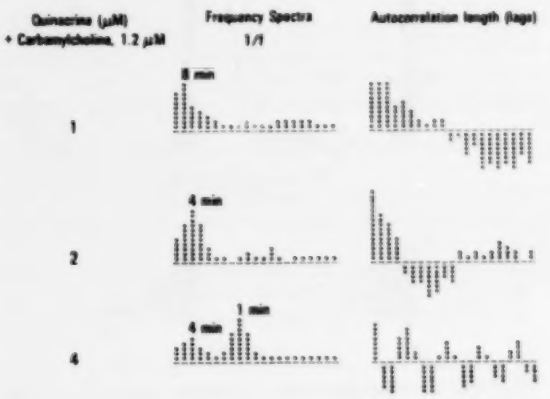

FIGURE 2. Spectra and autocorrelation functions showing shift from equilibrium behavior to subpopulation "bursting" associated with loss of response to cholinergic agonist in a population of cholinergic receptors. *See* text.

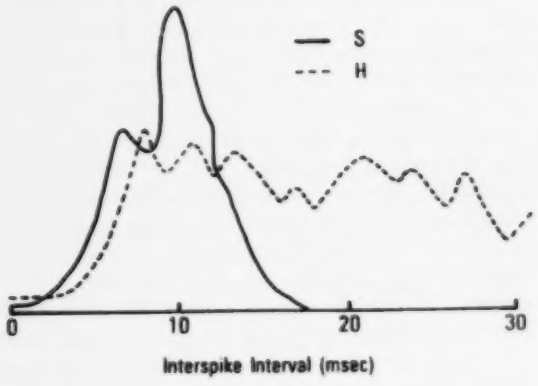

FIGURE 3. Distributions of interspike intervals in spinal cord interneurons during response habituation, showing distinction between those that manifested a single population distribution and those that contained a multiplicity of frequency-labeled populations. *See* text.

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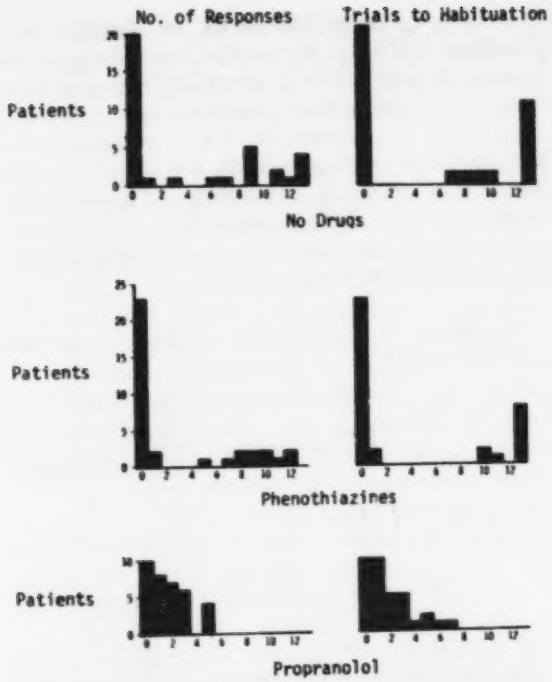

FIGURE 4. Characteristic response irregularity and failure of some schizophrenic patients to habituate an autonomically mediated skin conductance response to tones (Gruzelier 1978), showing the contrasting effects of phenothiazines and propranolol on those responses.

In Figure 4, data from Gruzelier (1978) show the characteristic response irregularity and failure of some schizophrenic patients to habituate an autonomically mediated skin conductance response to tones. The defect was not corrected by phenothiazines, but was normalized by either d- or l-propranolol (Gruzelier 1979). That the d-isomer was as effective as the l-isomer suggests that β-receptor blocking is not the mechanism of this effect. Recent work (Figure 5) suggests that both d- and l-propranolol can phase a significant portion of the kinetic variations of nigrostriatal dopaminergic tyrosine hydroxylase into a strong single rhythmic peak—perhaps coupling previously disparate populations into a more harmonically functioning whole (Mandell & Russo 1981).

It would be interesting indeed if the split-mind implied by the name of the schizophrenic syndrome were, in some cases, from a dynamical systems point of view, literally correct. It was Pavlov (1928) who first saw the deep relationships among the post-habituated state of "internal inhibition," the chronic "inhibitory condition" of schizophrenic patients, the functional cortical hemispheric splitting involved in dissociative phenomena, and the schizophrenic syndrome as resulting from the "destruction of the normal unification of the activity of the whole cortex."

It is hoped that this example suggests that the present era of qualitative mathematical description of the behavior of complex and dense systems promises a language for a scientifically based attempt at the fusion of clinical psychiatric phenomenology and neurobiological mechanism. Especially exciting is the possibility that infinite dimensional control and state spaces may be characterized by measures of low dimensional dynamical structure.

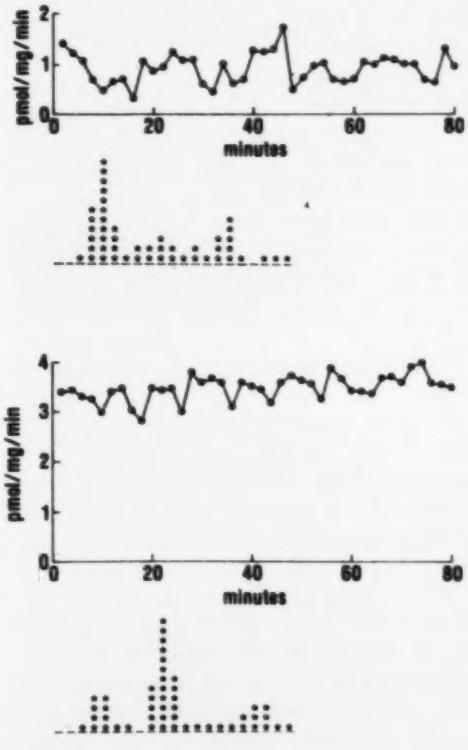

FIGURE 5. Time series containing median values from 80-minute time courses of tyrosine hydroxylase kinetic behavior. The top graph shows a typical control; the bottom graph reflects the faster, more regular periods induced by 5 μM propranolol.

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Interaction Among Government, Industry, and Extramural Investigators: New Developments and Problems

Co-Chair **Arthur Rifkin, M.D.**
The Mount Sinai School of Medicine
New York, N.Y.

and

Barrett Scoville, M.D.
National Institute of Neurological Disease and Strokes
Bethesda, Md.

An Investigator's View

Arthur Rifkin, M.D.

The purpose of this study group was to discuss problems and solutions in the interaction among government, industry, and investigators in the development and clinical testing of new drugs, and in the evaluation of the results of drug research. Different opinions exist among these groups about the balance between scientific purity and clinical exigencies, the government's role in promoting or directing the development of drugs, and other issues involved in characterizing new therapies.

The aim was not merely to air dissatisfaction, but to state what the problem was and what should be done about it. The most optimistic expectation was that a consensus on some issues which may influence the future policy would be reached.

In recent years the protocols coming from the drug companies have been much more sophisticated in methodology, an improvement investigators welcome. This results from the growing recognition that approval of new drugs or new indications for old drugs should hew to a higher standard than before. One can usually date a clinical trials paper by its methodology alone as optimum technique changes. For example, the need to define diagnosis by atheoretical operational criteria, and to define relapse and remission in equally empirically operational terms, methodology absent in the most elegant of early studies, are now accepted as necessary. The usual competitive drives of the three players in this field—industry, government, and investigators—have combined to pursue excellence. The investigator wants his work to be believed and to be influential. To accomplish this, he must impress his peers with the adequacy of his methodology and the data analysis. How discouraging it is to be faced with a challenge to data and conclusions after months to years of work because of what others consider flaws in design or analysis. It is clear that the investigator has an interest in the tightest methodology and data analysis.

The drug company's interest, let us assume nothing more than unbridled capitalism, is to sell its product. To do this it needs a good drug to sell, it must convince the FDA of its safety and efficacy, and it must persuade the physician to prescribe it. The cost of developing and promoting a drug is enormous. It must be in the interest of the company to assure itself that its new drug or new indication is really going to work. Too often persons outside of the industry focus on its marketing aspect, which is far removed from scientific issues and easy to ridicule. They wonder if the rose of Ludiomil will sell better than the butterfly of Sinequan. Marketing aside, however, the first question facing those in the corporate boardrooms is whether the drug really works and is reasonably safe. Only if that question is answered affirmatively can they go forward and consider questions of marketing. Therefore, it is in industry's self-interest to encourage the use of the most accurate methodology and data analysis.

The third leg of this tripod, the FDA, also has

its vested interest in clinical accuracy. So then, if everyone is interested in the best methodology, where is the problem?

There are some divergent interests among these groups. On the industry's side, they want as smooth sailing as possible once they are convinced that the drug works and that it is marketable, and they chafe at bureaucratic restrictions. They pressure investigators to live up to FDA standards even if they think them excessive in order to facilitate approval. The FDA is not interested in the drug company's profit, but only in protecting the public from ineffective or unsafe drugs, so they are interested in the most pure methodology.

The investigator has a responsibility shared by none of the other two partners in bringing new drugs out: he must take care of a sick person. Most improvements in methodology have been at the expense of the ease of following usual clinical procedures. In "the bad old days," making a diagnosis did not require laboriously completing scales such as the Schedule for Affective Disorders and Schizophrenia (SADS), and counting off symptoms, and making sure that all raters understood clearly and equally the distinction between thought insertion and delusions of reference. The rating scales are longer and are used more often. Diagnostic distinctions are much more careful. We are much more likely to bother the patient with requests for body fluids. All these techniques cost something that is often not apparent to those not on the firing line of obtaining data. They cost the acceptance and compliance of the patient. Without research subjects, this whole enterprise founders, so the investigator is in the position of fighting back against the FDA and the drug company, who want more purity, because the investigator fears he will lose his subjects by annoying them too much. In these days of declining interest in psychiatry by medical students, and in declining availability of money for training and research, the clinical investigator may be an endangered species. It somehow seems easier to do things in studies the further away you get from the patient.

Two issues have come up recently to make life difficult for the investigator.

It is becoming customary to insist that the blind psychiatrist treating the patient and obtaining the research data not learn which treatment his patient received until the entire study is completed. The reason is that if he learns, for example, that patients on Treatment A do better than those on Treatment B, that may bias his future ratings, especially if he thinks he can, or actually can, distinguish the treatments by their adverse reactions. There is some face validity to this, but consider the clinical consequences. If we are comparing an antidepressant to placebo, what does the clinical investigator do with the patient when he completes the trial? If he responded and received placebo, the clinician would not want to continue drug treatment. If he responded and received the active drug, the best clinical treatment would be to continue the drug openly and not risk relapse by switching to another drug. If the patient did not respond and received placebo, we might choose a different drug for followup care than if he did not respond to an active drug—or a supposedly active one. For example, if the experimental drug is a new tricyclic antidepressant (TCA), we might not wish to try another TCA, but switch to a monoamine oxidase inhibitor or electroconvulsive treatment.

When confronted with this problem, the investigator asks the drug company what it expected him to do with the patient who completed. The answer usually is to put completers on a moderate dose of another antidepressant. This is unreasonable. The patient who had responded to the experimental tricyclic, who gets a lower dose, might relapse; the patient who had not responded to the experimental drug would continue to get a possibly ineffective treatment. The placebo patient who did respond would get a moderate dose of an antidepressant abruptly—unnecessary treatment.

A more common situation would be a comparison of a new antidepressant with a standard one. Similar problems arise if the investigator tries to keep the treating psychiatrist blind and yet able to continue to treat his patient. If the investigator switches everyone who finished the study to a moderate dose of the standard antidepressant, the following would occur:

1. The patient who responded to the experimental drug would be abruptly switched to another;
2. The patient who responded to full dosage of the standard drug would be switched abruptly to a lower dose;
3. The patient who did not respond to the ex-

perimental drug would be switched abruptly to another perhaps similar drug;

4. And, worst of all, the patient who did not respond to full dosage of the standard drug would be switched to a lower dose and face another 6 weeks of ineffective treatment.

Similar unpleasant scenarios could be given for other types of drug trials.

The only way out that this writer could devise was to abruptly switch psychiatrists when the subject finished the study, keeping the first psychiatrist blind and free to continue to treat other patients in the study, while the second psychiatrist broke the blind and received other patients as they finished the study, i.e., a two-platoon system of psychiatrists

To do all this maneuvering for the sake of the possibility of bias, if the treating psychiatrist breaks the blind as each patient completes, seems to be an example of methodological purity exceeding its bounds.

Another way of avoiding this conflict of interest is to use blind clinical raters and unblind psychiatrists. This is possible, but not perfect: the unblind psychiatrist may adjust dosage differently if he knows he is prescribing an experimental or standard drug, i.e., he may tolerate more adverse reactions of the standard drug. It is more expensive to use clinical raters if the research must pay for both the clinical rater and the psychiatrist.

Another area of difficulty is the use in some recent protocols of the provision that if the dose is lowered, it cannot again be raised because the change in adverse reactions may tip off the blind psychiatrist to whether the drug is active or placebo, or even which of two active drugs is being taken according to differential adverse reactions. This restriction will lead to two results: the blind psychiatrist will be loath to reduce dosage knowing he can not go up again, and be left giving an inadequate dose so that the subject will perhaps suffer needlessly or drop out; or the blind psychiatrist will lower the dose and threaten the accuracy of the study's attempt to answer a clinical question because of insufficient exposure to drugs.

This is another example of trying to restrict the freedom of the investigator for the sake of purer science, but actually losing more than gaining, because the impact on the clinical situation was not adequately considered.

Industry's Response to New Drug Developments

Victor B. Slotnick, Ph.D., M.D.[1]

The pharmaceutical industry maintains an ongoing interaction with the Food and Drug Administration (FDA), clinical investigators, and academia. The following are some examples of interactions that have involved the FDA.

About 5 years ago, the company was planning to initiate a 400-patient program to assess the long-term safety and efficacy of a neuroleptic in chronic schizophrenic outpatients. The patients in this program were to be treated in double-blind fashion for 12 months. During the year of treatment, each patient was to have 10 psychometric assessments. The paperwork involved in collecting efficacy data for each patient consisted of the following: Twenty Brief Psychiatric Rating Scale (BPRS) sheets (10 assessments x 2 sheets per assessment), 10 sheets of outpatient functioning assessments, and 10 sheets of Clinical Global Impressions (CGI) assessments. The total was 40 sheets of paper for each patient.

In discussing the potential paper load with the FDA, company representatives suggested supplying one summary sheet with raw efficacy data for each patient. The FDA agreed with the proposal; however, they recommended the following: 1) that the raw data for each patient be transcribed to the summary sheet after each patient completed treatment; 2) that the senior investigator sign the raw data summary sheets after transcription; and 3) that the investigator keep the original psychometric assessments for the appropriate period of time. The volume of paperwork for each patient's case report form was thus reduced by about 80 percent.

Turnaround Time of Submission to the FDA

Over the last year or so, the company's experience with regard to the amount of time the

[1]Clinical Investigation, McNeil Pharmaceutical, Spring House, PA 19477.

FDA has taken to respond to submissions has been encouraging.

In October 1980, a New Drug Application (NDA) for a neuroleptic with data for about 800 patients was submitted. In January 1981 the company received a written request for additional information and a request to meet with the FDA. Company representatives met with the FDA to discuss the NDA and requested that the NDA be presented to the FDA and its Advisory Committee in April. Although there was no definitive outcome from presentation to the Advisory Committee, it was heartening to experience a review of an NDA with an Advisory Committee presentation in a period of slightly less then 6 months.

In late October of this year, the company submitted a supplemental NDA to the Division. About *10 days later,* the company received a letter from the FDA indicating that the supplemental NDA had been reviewed to a limited extent and the Division felt that the submission should be transferred from supplemental NDA status to NDA status. Although the review of the NDA is still in progress, information apprising us of the status of our submission was obtained from the FDA in a relatively short period of time.

About 6 weeks ago, the company submitted a special clinical safety report for an investigational neuroleptic to the FDA. A copy of the report was hand-carried to the FDA the morning of the day of submission. That afternoon, the FDA contacted our Regulatory Affairs personnel with questions and comments concerning that submission—a same-day response.

Requests from Investigators for Clinical Supplies

During the past several years, the company has received many requests from physicians for clinical supplies. Most of these requests have been for placebos to match oral or injectable dosage forms of the company's commercially available drugs. About 1 1/2 years ago, the company implemented a policy about such placebos: they are considered to be investigational drugs. In order to obtain placebos to match marketed drugs, an investigator is required by the company to file with the FDA and obtain an individual investigational new drug (IND) number. In general, the investigators requesting placebos have cooperated with this policy.

Compassionate INDs

A working definition of a "compassionate IND" is as follows: A request by a physician to the FDA to treat a patient who has a specific life-threatening or non-life-threatening clinical condition with an investigational drug. It should be noted that the current FDA regulations make no mention of compassionate INDs. It is a fairly safe assumption that most pharmaceutical companies represented in the audience receive a fair number of requests for their investigational drugs to be used in compassionate clinical situations.

About a year ago, McNeil received a special request from one division of the FDA concerning compassionate INDs. It appeared that this division had received many requests from individual physicians requesting to study a McNeil investigational drug in two non-life-threatening compassionate clinical conditions. Because of the increased workload for the FDA, they requested that McNeil file the paperwork for those individual physicians under the company's IND for that drug.

However, an informal survey of medical colleagues revealed that other divisions of the FDA permit physicians to file directly with the FDA in order to obtain a compassionate IND.

Although McNeil was not averse to working with the Neuropharmacology Division, the problem could have been handled satisfactorily with less burden placed upon the sponsor if the Division had given McNeil a special IND number for those compassionate studies with the provision that the IND be supplemented with those physicians wishing to use the investigational drug. In all fairness, it must be added that the Division did bend a bit. At McNeil's request they allowed a reduction of the frequency of monitoring visits by the company's clinical research support staff.

Physician-Investigator Without an Institutional Review Board (IRB)

In July of 1981, the FDA published a new regulation to the effect that physicians treating patients with investigational drugs outside an

institutional setting are required to have IRB approval for their studies. Most of the clinical investigators in the audience probably do not fall into this category because of their institutional setting. However, and perhaps more commonly in areas other than psychopharmacology, many private practice physicians interested in conducting investigational drug studies do not now have IRBs available to review their protocols.

In anticipation of the above regulations, and prior to their publication in the *Federal Register*, McNeil Pharmaceutical set up and organized an independent IRB in the area near McNeil. The Spring House IRB became operational in September 1981.

The Spring House IRB, in addition to protecting the patient, serves the following purposes:

1. to make an IRB available to any private practice physician interested in conducting a study with an investigational drug protocol for McNeil Pharmaceutical;
2. to reduce the cost for the approval of an investigational drug protocol; and
3. to reduce the time required for review and approval of an investigational drug protocol.

The Balance Sheet (The Other Side of the Ledger)

Paul Leber, M.D.[1]

Alistair Cooke, the noted TV essayist, once asked a bootblack, who was on the eve of his retirement, what he had learned about life in America during the many years he had shined shoes in the corridors of New York's Grand Central Station. The man, who had immigrated from Europe as a child some 70 years earlier, said without a moment's hesitation "In America, there is no free lunch!"

The bootblack clearly understood a basic principle, not, of course, unique to American soil, that you rarely get something for nothing. It is interesting to examine how this "natural" law applies to our attempts to respond to the perceived public demand for less costly and more efficient new drug development and approval.

[1]Food and Drug Administration, Rockville, MD 20857.

In general, costs are conceived in terms of either time or money. In the course of clinical drug development, costs are obviously affected by the number of subjects studied, the complexity of clinical trial design, and the task and cost of data analysis. For example, increasing the complexity of the clinical trials (i.e., adding more kinds of observations and having them made more often by several independent raters) will obviously increase costs. Moreover, the subsequent analysis of data collected from large and complicated trials will also be more difficult, more expensive, and more time consuming. Sheer numbers count, too! While it is conceivable that the cost per subject or cost per individual study may fall as the absolute numbers of patients and studies increase, it is safe to assume that, other factors held constant, a new drug application (NDA) based on 20 Phase III studies enrolling 1,000 subjects will cost more than one with 10 studies enrolling 500 patients.

Given these facts, it is not surprising that, in the face of a public mandate to reduce cost, both the Agency and commercial sponsors will consider the feasibility of reducing (1) trial design complexity, (2) the number of subjects studied, and (3) the cost of data analysis in the preapproval/premarketing phase of new drug development.

This is all well and good, but recall that there is no free lunch! Pay less; get less!

It is the author's purpose to focus your attention on the other side of the balance sheet not pass judgment on the specific items involved nor judge the relative merits of the assets and debits entered. He wishes only point out that changes in one side of the ledger require changes in another part.

First the obvious. If fewer subjects are studied during the premarketing phase of new drug evaluation, our ability to detect relatively low frequency adverse or untoward drug effects will be decreased. A quick calculation illustrates any point. To be 95 percent certain of detecting at least one example of an event which occurs at an incidence of 1 per 100 patients treated for 1 month at some effective dose level of a drug, 300 patients must be observed at that dose (or a higher one) for the month. This figure is derived assuming a Poisson distribution of rare events. For general use, a good rule of thumb is that the number of subjects studied must be equal to three times the

reciprocal of the estimated event rate (i.e., 300 for an incidence of 1 per 100, 1500 for an incidence of 1 per 500).

Again, the author is not passing judgment; he is merely emphasizing that if we elect to study fewer patients before a drug is approved, one should not be surprised if a relatively common adverse event is reported during postmarketing experience which was not detected during premarketing drug trials. *Parenthetically, the FDA is well aware of this problem and is actively expanding existing and developing new postmarketing surveillance strategies and programs.*

In contrast to safety, drug efficacy is determined in an absolute sense and is thus less likely to be affected by current trends toward smaller sample sizes. Thus, sample size can only be reduced to the point that the potency of the drug (that is, its efficacy) will allow.

Experts today are, in the author's opinion, even more exacting than in the past about what kind and quality of evidence collected from controlled clinical investigations is persuasive and substantial (i.e., evidence sufficient for drug approval). Thus, a modest drug, which is only slightly more effective than placebo, may require that many more subjects be studied to establish its efficacy than a potent drug would. One caveat, the author is not speaking to the issue of the magnitude of clinical effectiveness declared clinically meaningful. Rather, his comments assume that a small mean difference observed or produced by a modest drug is clinically meaningful and that it will thus require more subjects to demonstrate the statistical significance of this mean difference than it would if the mean difference were large.

There is a chance, of course, that when cost is the determining factor, it may prove more economical to use sophisticated multivariate statistical techniques to establish statistical significance than to enroll more patients or to conduct additional trials.

One problem arises when fewer subjects are studied, however, that has not often been discussed but deserves consideration and attention.

It is far simpler to demonstrate that a drug is active and efficacious than it is to describe, in detail and with precision, for whom it should be used and under what specific conditions. You may all recall that our regulations require that a prescription drug's labeling (professional package insert) provide the practitioner with adequate directions to use the drug in the population for whom it is intended.

The fewer patients studied in the premarketing phase of drug development, the more difficult it becomes to provide detailed and precise directions for the use of the drug.

Several of you were present at the recent Psychopharmacologic Drugs Advisory Committee meeting on December 3-4. You saw the advisory committee struggle with this very issue. Although convinced that two new antidepressant drug products were efficacious, it was difficult to describe, in detail, precisely for whom and under what conditions each drug should be used. It is obvious that current diagnostic categorizations (which have become possible with advances in the understanding of depressive disease) make it even more difficult to describe drug use with small numbers of subjects and limited number of trials.

In an idealized world, with an infinite amount of time, and where money was no object, we could block subjects on every diagnostic feature of potential interest and, conducting extensive trials of complicated design, determine precisely what portion of the potential patient population should take a new drug, and what would happen to them. Then we could write very complete and accurate drug labeling. But, as the English novelist Butler suggested approximately 100 years ago, *life is the task of drawing satisfactory inferences from inadequate premises.* If we are to follow the public mandate for less costly and speedier drug approval, we may have to accept broader labeling inferences from smaller and perhaps narrower data bases. Just how much smaller and how much narrower is an issue many of you in the audience will help decide while serving in your roles as our official advisors and outside experts. The issues involved are broad and beyond those covered by law. It is clearly a matter of informed judgment how much must be known about an active and efficacious drug before it is introduced into the market place. These are the questions we will all have to answer.

It is useful to remember, too, that there "is no free lunch." If we extensively modify the new drug development process as is now being actively considered in order to expedite the development and approval process of new drugs, a complete understanding of a new drug's best use may have

to come from postmarketing experience and reassessment of the drug's benefit/risk ratio. Remember, there are no absolutes in this process. Words and phrases like "well controlled" and "substantial" and "adequate direction for use" are determined by the opinion of experts as much as by law. The FDA looks forward to your careful consideration and counsel on these important issues.

New Biological Approaches to Schizophrenia

Co-Chair: Philip A. Berger, M.D.
Department of Psychiatry and Behavioral Sciences
Stanford University School of Medicine
Stanford, California

and

Jack D. Barchas, M.D.
Department of Psychiatry and Behavioral Sciences
Stanford University School of Medicine
Stanford, California

Dopamine Neuronal Instability: A Model for the Schizophreniform Psychoses[1]

Roy J. King, M.D., Ph.D.,[2] Joachim D. Raese, M.D.,[2] Bernard A. Huberman, Ph.D.,[3] and Jack D. Barchas, M.D.[2]

The dopamine model of schizophrenia predicts that an excess in dopamine (DA) causes psychotic symptoms. Such a simple excess is not confirmed by the observed behavior of schizophrenics. Bleuler (1950) noted that schizophrenic individuals often manifest rapidly alternating and mutually contradictory affect, thought, and activity. Ellinwood et al. (1974), after injecting amphetamine chronically to cats, found a desynchronization and a fragmentation of their stereotypic behavior. Moreover, experimental evidence has not revealed an increase of dopamine function in schizophrenics. The authors propose here that, rather than an excess of DA, psychotic individuals exhibit an instability in dopaminergic function. This instability would be caused by an excessive dopaminergic feedback. Since the dopaminergic system appears to be well modulated with a variety of feedback mechanisms, including long-loop neuronal feedback, short-loop local inhibitory feedback, and regulation of dopamine synthesis through the activation of tyrosine hydroxylase, these mechanisms may be more crucial in determining psychotic symptoms. It is well know that systems with a high degree of negative feedback are relatively insensitive to slow changes in internal parameters or external input. However, they may become unstable with increasing feedback. These instabilities fall into three major classes:

1. the appearance of multiple equilibrium states;
2. the creation of autonomous oscillations; and
3. a chaotic behavior with a sensitive dependence on initial conditions and unpredictable variations in state.

It has been mathematically demonstrated that modeling the currently known feedback mechanisms of the dopaminergic system will lead

[1]This study was supported by USPHS Grant MH-23861 from the National Institute of Mental Health and by the Scottish Rite.
[2]Nancy Pritzker Laboratory of Behavioral Neurochemistry, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA 94305.
[3]Xerox Palo Alto Research Center, Palo Alto, CA 94304.

to the appearance of these instabilities (King et al. 1981). Herein the authors summarize the relationship between these instabilities and offer predictions about schizophrenic behavior. DA feedback mechanisms involve several time constants: neuronal feedback, occurring rapidly over a period of 1/3 to 2 seconds, activation and deactivation of dopamine synthesis proceeding over periods of 10 to 20 minutes, and long-term up-and-down regulation of dopaminergic receptors occurring over periods of days to weeks. The proposed increased feedback in psychotic individuals will lead to instabilities of behavior on all three time scales. This increased feedback can occur through a variety of mechanisms. For example, an increased release, decreased reuptake, increased synthesis, or increased postsynaptic DA receptor activity will all lead to an increased feedback gain. Likewise, an increased autoreceptor activity, a decreased DA synthesis, or a postsynaptic blockade of dopamine receptors will result in a net decreased feedback. Thus, the former procedures will lead to instability, whereas the latter modifications will rectify that instability. The authors now describe the effect of changing these parameters on the dynamical behavior.

One-third to Two Seconds. Because of the delays in activating and deactivating postsynaptic DA and GABA receptors, a simple stable equilibrium of dopaminergic activity can, by increasing feedback gain, bifurcate into periodic oscillations in dopaminergic firing. These oscillations will have a frequency of the order of the time constant for the delay, that is, 3 Hz to 1/2 Hz. Because the dopaminergic system projects directly to various regions of the limbic system and the striatum, and indirectly projects through the pars reticulata of the substantia nigra to the brainstem, one might expect that psychotic individuals would exhibit this periodic disturbance in activity. Such fluctuating activity has been reported by Ellinwood et al. (1974) in cats treated chronically with amphetamine and by Heath (1954) in subcortical recordings of electrical activity in schizophrenics. Behaviorally this autonomous slow-wave activity might manifest inself, for instance, in the thought disorder, perceptual changes, and eye-tracking disturbances observed in some schizophrenic patients.

Ten to Twenty Minutes. The dopaminergic system is unique among the monoamines in that with both an increase and a decrease in firing, there is an increased activation of dopamine synthesis (Nowycky & Roth 1978). It can be shown that for greater than a fourfold increase in dopamine synthesis at low firing rates, the single homeostatic equilibrium of the dopaminergic system will bifurcate into two stable equilibria. One of these equilibria has a relatively high mean DA output while the other has a lower DA activity. The low dopaminergic state will progressively, with increasing long-loop feedback gain, bifurcate further into oscillations and chaotic activity. This periodic or erratic activity will have a time constant of around 10-20 minutes. In addition, since the dopamine nuclei appear to be loosely coupled, that is, an activation of the one substantia nigra results in a deactivation of the contralateral substantia nigra (Nieoullon et al. 1977), this chaotic activity may decouple the left substantia nigra from the right substantia nigra or a substantia nigra nucleus from a ventral tegmental dopaminergic nucleus. One might, therefore, observe rapid transitions between high and low dopaminergic states as well as spatially decoupled simultaneously activated and deactivated dopaminergic states. This prediction may agree phenomenologically with Bleuler's reports on schizophrenic ambivalence of affect, will, and thought.

Furthermore, the addition of amphetamine, although initially causing a transition from a normal to a chaotic state, could remove a DA nucleus from a chaotic state and place it in a relatively stable high DA activity state. This might explain some of the results reported by van Kammen et al. (1980) on the stabilizing effect of amphetamine given to acutely psychotic individuals.

Days to Weeks. With the bifurcation of DA activity into a low and high DA state, long-term, up-and-down regulation of DA receptor activity could result in oscillations of dopamine function over a period of days to weeks. This behavior can take the form of either bistable oscillations or pulses with rapid transitions from a low to a high DA state. This would be followed by a plateau in DA activity, leading ultimately to a sudden post-plateau drop in DA activity at levels lower than those of the initial DA state. Antleman and Chiodo (1981) have shown that chronic amphetamine, tricyclic antidepressants, and rapid-eye-movement (REM) sleep deprivation may all

lead to a subsensitivity of the dopaminergic nigral autoreceptors. Since a decrease in the sensitivity of the autoreceptors causes a net increase in feedback gain, these procedures could lead to a rapidly cycling transition between low to high DA states. Furthermore, if the feedback gain is initially large, the transitions between the low and high dopaminergic states will be chaotic and weakly correlated with transitions from low to high dopaminergic states in other dopaminergic nuclei. Such behavior might be similar to that of an acute schizophreniform psychosis. The schizoaffective psychoses additionally could manifest themselves in oscillations between high and low dopaminergic states that are relatively unsynchronized between neighboring nuclei.

In summary, it is proposed that psychosis results from an excessive DA long-loop feedback. The gain of this feedback circuit can be modified through a variety of mechanisms. Because of the large feedback, a schizophrenic and a nonschizophrenic individual may not differ in the mean values of any parameter monitoring DA activity. However, as a result of the increased instability in DA function, the psychotic individual will show greater spatio-temporal variability in DA activity. On a time scale of seconds, this instability will result in oscillations of neuronal activity that can spread to various subcortical and cortical regions. Over a period of minutes, DA activity will bifurcate into multiple stable states, periodic oscillations, and chaotic activity. On a time course of days to weeks, long-term regulation of DA receptor density can lead to the precipitation of that chaotic or oscillatory behavior. This model is consistent with a variety of genetic and environmental factors leading to a common instability in dopaminergic function.

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Retinal Oscillatory Potentials in Schizophrenia: Implications for the Assessment of Dopamine Transmission in Man[1]

Joachim D. Raese, M.D.,[2] Roy J. King, M.D., Ph.D.,[2] Debbie Barnes,[3] Philip A. Berger, M.D.,[2] Jack D. Barchas, M.D.,[2] Michael Marmor, M.D.,[3] and Peggy Hock, Ph.D.[3]

Recently, a new formulation of the dopamine (DA)-hypothesis of schizophrenia has been presented which shows that for certain unstable properties of dopaminergic feedback loops a spatial and/or temporal desynchronization will occur resulting in fragmentation of a dopaminergic nucleus into clusters of cells locked into high and low firing states (King et al. 1981, in press). This restatement of the DA-hypothesis does not predict net changes in DA or its metabolite concentrations.

This hypothesis was tested by examining the properties of the light-evoked oscillations in the

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[2]Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA 94305.

[3]Department of Ophthalmology, Stanford University School of Medicine, Stanford, CA 94305.

Address correspondence to Dr. Raese.

retina which can be recorded from the anesthetized cornea. The rationale for this approach is based on several observations: 1) The mammalian contains a substantial concentration of DA (Haggendal & Malmfors 1963) as well as tyrosine hydroxylase (Juvone et al. 1978a, 1978b; Juvone & Neff 1981) in the amacrine cell layer. Retinal tyrosine hydroxylase is rapidly activated by exposure of the eye to light (Juvone et al. 1978a, 1978b). The activation is associated with kinetic changes of the enzyme identical to those occurring in nigrostriatal neurons (Nowycky & Roth 1978). 2) The activation of tyrosine hydroxylase is inhibited by gamma-aminobutyric acid (GABA) (Morgan & Kamp 1980) located together with DA-containing neurons in the amacrine cell layer, suggesting a DA-GABA feedback loop similar to central DA-GABA synaptic connections (Nowycky & Roth 1978). 3) DA-receptors modulate DA-turnover in the retina in a way which is analogous to the brain, i.e., dopamine-blocking drugs such as neuroleptics will increase, and activation of presynaptic receptors by apomorphine will decrease DA-turnover (Wassenaar & Korf 1976). 4) DA-depletion of the retina by reserpine will abolish the oscillatory potentials (OPs) in the rabbit (Hempel 1972-1973) which can be restored by intravitriol injection of the DA-precursor l-DOPA (Gutierrez & Spiguel 1973). The GABA antagonists bicuculline and picrotoxin also abolish the OPs (Wachtmeister 1980), indicating that both intact DA and GABA transmission are necessary for the OPs to be elicited.

In this paper, data are presented which suggest that the OPs are modulated by dopaminergic activity in man. The investigators' approach consisted of: 1) a detailed statistical comparison of waveforms obtained from normal volunteers and drug-free schizophrenic subjects; and 2) stimulation of DA-transmission by amphetamine.

Methods

All patients participating in the study were men (ages 28-58) hospitalized at the Clinical Research Center at the Veterans Administration Medical Center in Palo Alto, California. The patients were managed without use of psychotropic medication for 2 weeks prior to the study. They were given diagnoses of schizophrenia or schizoaffective psychosis using Research Diagnostic Criteria (Spitzer et al. 1978) by three clinicians independently. Patients gave informed consent to the study, which was approved by the Committee on Research on Human Subjects at Stanford University. Patients were rated weekly by two clinicians using the Brief Psychiatric Rating Scale.

Subjects received intraocular drops into the right eye of mydriacyl and neosynephrine to maximally dilate the pupil. After dark adaptation of the eyes for 20 minutes, surface anesthesia was induced by applying novesine drops to the eye, and a contact lens (Burien-Allan) fitted with electrodes was placed on the cornea. A light source (Grass) was placed 25 cm from the eye, its power supply set to maximal intensity (W16), and light stimulation was carried out in 10-second intervals by triggering the lamp and simultaneously a sweep of 100 msec duration on a storage oscilloscope (Tektronix). Oscillatory potentials were recorded using a frequency filter attenuating frequencies below 100 Hz. Traces stored on the oscilloscope screen were photographed using a Polaroid camera.

The negative and positive deflections constituting the retinal light-evoked response were measured as shown in Fig 1-A and will be referred to as Relative Amplitudes (RA). Positive RA were assigned the labels 0[1], 0[2], and 0[3] in order of their latencies from the stimulus. Similarly, negative RA were termed N[1], N[2], and N[3] such that the alternating positive and negative RA of the waveform are described by the sequence $0[1] - N[1] - 0[2] - N[2] - 0[3] - N[4]$ (Figure 1-A). Latencies were measured as shown in Fig 1-B by determining the distance from the first negativity to the first peak 0[1] and assigned the label $\Delta 0[1]$. The distance representing the time elapsed from 0[1] to the trough N[1] was termed $\Delta N[1]$, etc. $\Delta O[1]$ through $\Delta N[3]$ will be referred to as Relative Latencies (RL).

All values of Relative Amplitudes were scaled by calculating their natural log. These natural logs were used to calculate the means, standard deviations, and variance of 5 to 11 measurements of each RA in each subject. The grand pooled variance for the RAs 0[1] through N[3] was determined for eight normal subjects and nine schizophrenic patients utilizing between 55 and 70 measurements for each RA for each of the two groups

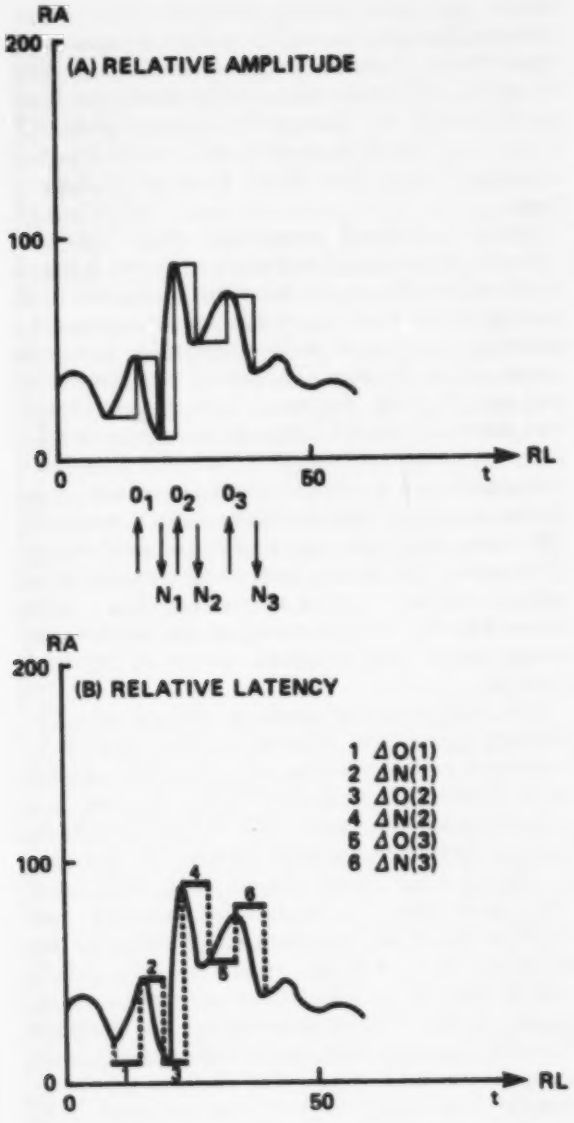

FIGURE 1. Determination of Values for the Major OP-Waveforms. We define the sequence 0[1], N[1], 0[2], . . . and A) determine the length RA = Relative Amplitude = PA_n-PA_{n-1}. B) Time (t) elapsed from stimulus (t = 0) is measured and the sequential periods labeled 1, 2, . . . 6 are assigned the labels Δ0[1], ΔN[1], . . .ΔN[3] = Relative Latencies.

Relative latencies were evaluated similarly except that unscaled values were used. Variances were compared by *F*-statistics, means by two-tailed *t*-test.

Results

Increased Variability of OPs in Schizophrenic Subject

Light stimulation of the dark adapted retina produces oscillatory waveforms characterized by increasing amplitude and stabilization of the oscillations in response to consecutive light flashes. Fig 2, A-C, illustrates that the OPs in three normal volunteers have stabilized after three light flashes.

Oscillatory potentials recorded from three schizophrenic patients are shown in Fig 2, D-F. Visual inspection reveals a lack of synchronization of the waveform.

In order to quantify this observation, the Relative Amplitudes and Latencies were determined as described in the Methods section. The Table shows the variances of RA and RL, respectively, of 11 normal and 11 schizophrenic subjects. Compared to normal subjects, schizophrenics had significantly greater variance of RA N[1] and N[3] while N[2] approached significance. The positive deflections 0[3] had similar variance in both groups. 0[1] and 0[2] had significantly higher variance in the control group. It should be noted that a major portion of this variance was contributed by one control subject who had extrememly high variance in this parameter. Interestingly, the subject has carried the diagnosis of dyslexia since childhood. This observation deserves further investigation.

The Table shows significantly higher variance in schizophrenia of RL ΔN[1] through Δ0[3], which corresponds to the time span encompassing the major OPs (*see* Figure 1, A and B), indicating that the time evolution of the central part of the evoked waveform is quite variable in schizophrenic subjects.

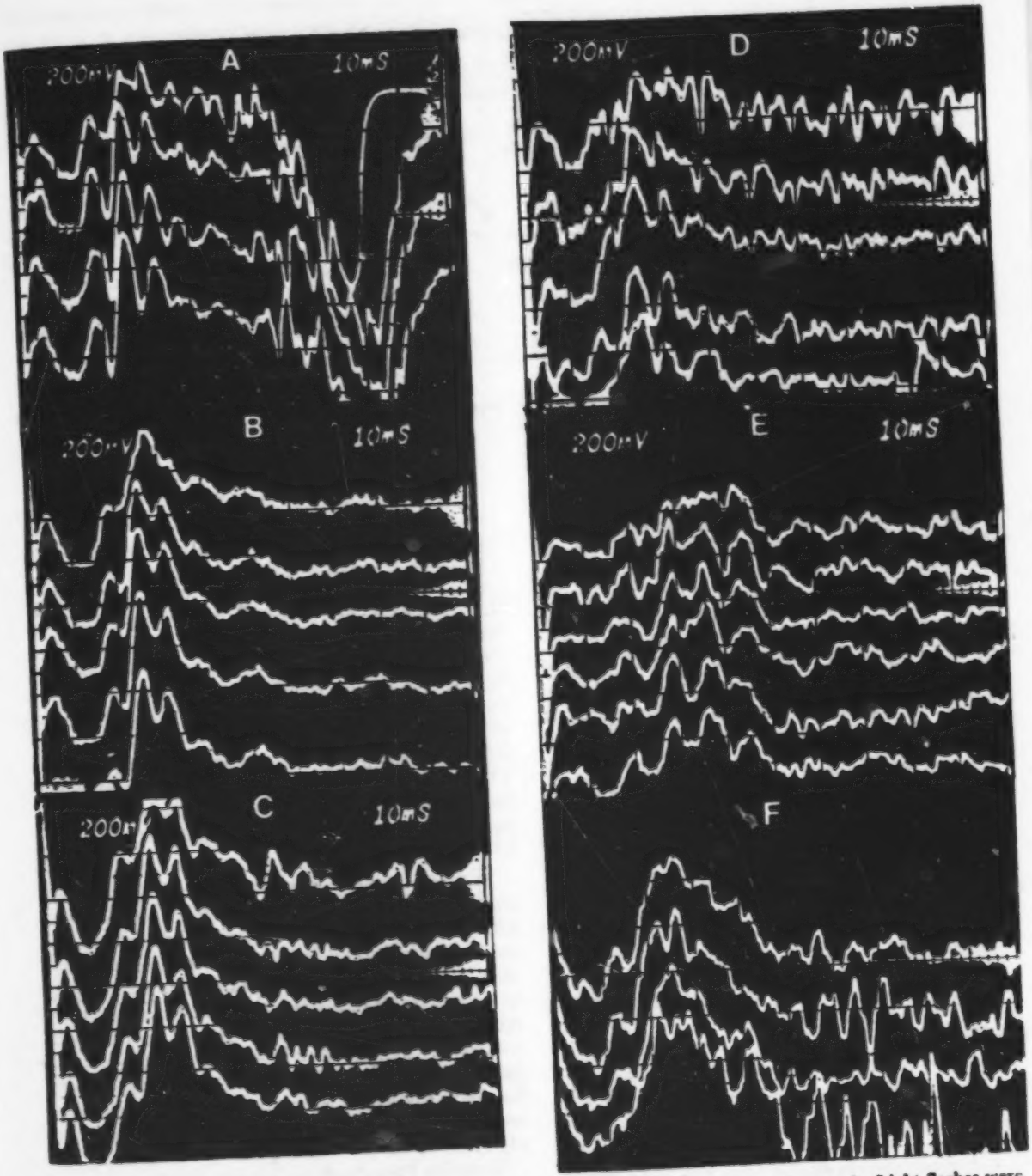

FIGURE 2. Oscilloscope Traces of Oscillatory Potentials. OPs recorded from three normal controls. Light flashes were given at a rate of 1 per 10 seconds. Sequence is from top to bottom of each panel (A - C). OPs recorded from three schizophrenic patients (D - F).

Table

Variance of Relative Amplitudes and Latencies of OPs

	Relative Amplitudes					
RA	O[1]	N[1]	O[2]	N[2]	O[3]	N[3]
Schizophrenia σ^2_p	.050	.150	.030	.190	.116	.073
Controls σ^2_p	.076	.106	.071	.142	.129	.043
$p<$	.026	.005*	.001	.08*	N.S.	.006*
	Relative Latencies					
RL	ΔO[1]	ΔN[1]	ΔN[2]	ΔN[2]	ΔO[3]	ΔN[3]
Schizophrenia σ^2_p	.012	.003	.008	.012	.003	.011
Controls σ^2_p	.012	.002	.003	.003	.002	.019
$p<$	N.S.	.05*	.001*	.001*	.05*	.005

*Schizophrenia > Controls
All others, Controls > Schizophrenia
Eleven controls and eleven schizophrenic subjects were studied and their OPs analyzed as described in the text. The variances (σ^2_p) of RA and RL values are shown. Significance was calculatec using the *F*-distribution.

Effect of Acute *D*-Amphetamine on the Relative Amplitude of the OPs

Baseline recordings were obtained from five subjects. One hour before their second recording they were given a single oral dose of 15 mg *d*-amphetamine. Amphetamine increased the mean relative amplitude (RA) of the oscillations (Fig 3) with the largest effects on O[1], N[1], and N[2].

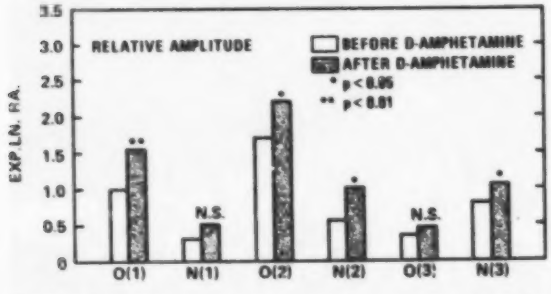

FIGURE 3. Effect of *d*-Amphetamine on the Relative Amplitude of Oscillatory Potentials. Two recordings were obtained from each subject. Subjects were given 15 mg of *d*-amphetamine orally 1 hour prior to their second recording session. The means of the natural log transforms of the RA obtained in the two sessions were calculated for each RA and compared by two-tailed *t*-test. Pre- and postdrug values of RA are plotted after exponentiation (exp. LN RA).

Discussion

Animal studies suggest that the OPs originate in deeper layers of the retina, the earlier potentials originating in different layers than the later ones, indicating a radial flow of current (Wachtmeister & Dowling 1978). In addition to this particular anatomical organization, the individual OPs are characterized by differential sensitivity to the GABA antagonists bicuculline and picrotoxin. The latter observation is consistent with the hypothesis that different transmitters may be modulating earlier and later OPs (Wachtmeister 1980).

In this study, the OPs were recorded from the cornea, i.e., at a great distance from where they originate. The recording represents, therefore, an integration of the activity of entire cell populations which must be firing synchronously in sequence in order to generate the oscillatory evoked response. This behavior is consistent with that of coupled oscillators time-locked to a stimulus. It has been suggested that the OPs reflect the radial flow of current through feedback loops connecting retinal layers of different depths (Wachtmeister 1980).

Since the OPs are dependent on the integrity of both DA and GABA transmission (Hempel 1972-1973; Gutierrez & Spiguel 1973;

Wachtmeister 1980), it is reasonable to assume a role for both transmitters in at least some aspects of their regulation.

Several findings are presented suggesting a modulatory role for dopamine in the generation of OPs in man:

1) *d-amphetamine, a compound known to enhance DA-transmission, significantly increased the amplitude of the OPs.* To the best of our knowledge, this is the first report of a direct effect of DA-transmission on the OPs of man.

There are only two brief reports on pharmacological manipulation of DA on the raw electroretinogram (ERG). A single oral dose of thioridazine (50 mg) caused a prolongation of the a-wave latency and b-wave evolution time, as well as a diminution of b-wave amplitude in normal volunteers (Filip & Balik 1978). The same group reported the lack of an effect of 500 mg L-DOPA on the same ERG parameters (Balik & Filip 1978). In neither study, however, were the OPs recorded.

Since the OPs ride on the ascending slope of the b-wave, it is conceivable that amphetamine could influence the OPs through b-wave changes. Examination of b-waves obtained pre- and postdrug treatment, revealed no significant increase or decrease of the b-wave (data not shown). This finding is in keeping with the observations that b-wave and OPs originate in different layers of the retina and that compounds such as GABA and glutamate, which profoundly affect the OPs, have no effect on the b-wave (Wachtmeister 1980).

2) *Schizophrenic patients have higher variance of OPs than controls.* The variance of the RAs of the first six negative and positive deflections of the OPs and the Relative Latencies in 11 control and 11 schizophrenic subjects were analyzed (Table). The negative RAs N[1], N[2], and N[3] had greater variance in the schizophrenic group. This "selectivity" militates against the argument that a "nonspecific" increase in noise could account for the desynchronized appearance of the OPs (Figure 2). The variance of the RL in the schizophrenic group is significantly increased in Δ0[2] through Δ0[3] which together constitute the major part of the entire waveform.

It should be pointed out that the increased variances of 0[1] and 0[2] in the control group are due to one control subject who had extremely high variances in these parameters. The subject had no psychiatric history but suffered from developmental dyslexia. Further studies will be necessary to decide whether there is a causal relationship of ERG parameters and that diagnosis.

Ranking the 11 patients according to their OP variance revealed that the major contribution of the pooled group variance was contributed by five patients, all of whom suffered from auditory hallucinations.

Although our total group size is small, this finding suggests the existence of subgroups of schizophrenic patients who may be differentiated by using the OPs record as criterion. This preliminary finding would suggest that desynchronized OPs may be associated with productive symptoms such as auditory hallucinations.

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A Convergence of Findings in the Psychophysiology of Schizophrenia[1]

Walton T. Roth, M.D.,[2] and Jared R. Tinklenberg, M.D.[2]

The history of the psychophysiology of schizophrenia has been similar to the history of other research approaches to this disease. Instead of steady progress over time, there have been sporadic reports of cardiovascular, electrodermal, EEG spectral, and, most recently, event-related potential (ERP) abnormalities that have proved minor, secondary, or unreplicable. Furthermore, there has been no theory to coordinate the diverse physiological measurements and give direction to experimental programs, except for the very general concept of activation or arousal, which is often applied in a post hoc fashion to explain whatever physiological differences are observed. Activation is probably more relevant to the understanding of anxiety states than to psychosis, though it would not be surprising to find high tonic levels of activation in patients whose psychosis has made them fearful.

Recently, a possible convergence of findings has become apparent that is consistent and unexpected. Skin conductance response (SCR) nonresponding and ERP P300 reduction have been observed in schizophrenic patients repeatedly in the last 10 years by groups of researchers who were quite unaware of each other's techniques, literature, and theories. That unawareness, though unfortunate in many ways, lends an element of independent verification to these findings, if a theoretical and empirical bridge can be built to show that the two phenomena have the same psychobiological basis.

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[2]Laboratory of Clinical Psychopharmacology and Psychophysiology, Veterans Administration Medical Center, Palo Alto, CA 94304 and Department of Psychiatry and Behavioral Science, Stanford University School of Medicine, Stanford, CA 94305.

Send reprint requests to Walton T. Roth, M.D., Psychiatry (116A3), VA Medical Center, 3801 Miranda Ave., Palo Alto, CA 94304, USA.

SCR is a transient decrease of skin resistance to novel or otherwise salient stimuli, usually measured on the palm where it has a latency of 2 or 3 seconds. The essential facts about SCR and psychosis are these:

1. SCR nonresponding is defined as responding once or not at all in a standard habituation paradigm with 75 dB sound pressure level, 1-second tones, and inter-stimulus interval (ISIs) from 25 to 45 seconds. According to this definition, 50 percent of schizophrenics are nonresponders, while only 15 percent of controls are nonresponders. Retarded depressives also have higher incidence of nonresponding than controls.

2. The ratio of evoked SCR/spontaneous SCR is much less for schizophrenics than for controls. This excludes simple arousal explanations.

3. Nonresponding schizophrenics become responders if the tone intensity in the habituation paradigm is increased or if a response is required.

4. Nonresponding schizophrenics are characterized clinically by emotional withdrawal, conceptual disorganization, and depressed mood.

5. There is some evidence that nonresponding is a trait: it has a higher incidence in preschizophrenics, and nonresponding schizophrenics continue to be nonresponders after clinical remission.

These assertions are based on investigations reviewed by Venables (1977) and Öhman (1981), who provide exhaustive lists of relevant references.

The phenomenon of nonresponding is extremely well-documented: at least five independent research groups in England, the USA, the Federal Republic of Germany, and Norway have observed it. Nonresponding is seen in both acute and chronic, medicated, and unmedicated patients, though not many first-episode, unmedicated schizophrenics have been tested. Although 15 percent of controls are nonresponders by standard criteria, these subjects may be nonresponders of a different kind than the majority of schizophrenics. Certain subjects fail to show SCRs to any stimuli, presumably because of innate differences that have no psychological meaning. More stringent criteria—for example, only considering subjects to be nonresponders if they evince "spontaneous" SCRs or SCRs to intense stimuli but fail to give SCRs in the standard habituation paradigm—may result in fewer false positives, i.e., nonresponding controls.

P300 by its designation is a positive ERP with a latency of about 300 msec. It has an amplitude on the order of 10 μV at a parietal midline location referenced to the ears or mastoids. Its latency and amplitude are not fixed, but vary widely according to the nature of the stimuli and the way the subject processes them. Table 1 lists 15 investigations of P300 in clinical groups. The investigations were carried out in eight independent laboratories in the USA, Canada, and the Federal Republic of Germany. P300 reduction is present in both unmedicated and medicated schizophrenics; however, as for SCR, few first-episode, unmedicated schizophrenics have been tested in P300 paradigms.

The most common paradigm for eliciting P300 has been designated the "oddball" paradigm in Table 1, following a usage in the ERP literature. The paradigm has the following properties: Two or more easily discriminable types of stimuli, often tones of two pitches, are presented repeatedly at a fixed ISI, usually between 1 and 3 seconds. One type of stimulus is less frequent than the other(s), and is usually made a target for a counting or reaction time (RT) task. These conditions are conducive to the generation of P300s to the infrequent stimuli, at least in normal subjects. Schizophrenics were found to have reduced P300s compared to controls in all paradigms except the two listed as 7C and 15, both of which deviated significantly from the oddball paradigm.

P300 reduction does not appear to be simply a reflection of poorer task performance on the part of schizophrenics. In Studies 6A, 10, and 13, differences remained even when performances were matched between groups. In Study 1, in which subjects were told to *ignore* the stimuli, the schizophrenic P300 reduction could be regarded as better performance since smaller P300s indicate that less attention was paid to the stimuli. However, the relation between ERPs and performance is a complex one, and the consequences of the reduced task involvement often found in psychotic experimental subjects are often subtle (for a review, see Roth, in press-a).

Are SCR nonresponding and P300 reduction in schizophrenics due to the same psychological or biological process? In the past 10 years a great deal has been learned about experimental

Table 1

P300 and Psychosis

Authors	Paradigm	Stimuli	Intensity	Probability	ISI (sec)	Results
1. Roth and Cannon (1972)	oddball, passive	noise, tone	70 dB SPL	.94/.06	1	P230: (S)chizophrenics < (C)ontrols for first 20 infrequents.
2. Levit et al. (1973)	guessing	noise, flash	30 dB HL	.50/.50	4-5	N1-P330:S < (D)depressed < C.
3. Verleger and Cohen (1978)	guessing (modeled after 2)	tone, flash	?	.50/.50	5-15	N1-P340:S < C.
4. Shagass et al. (1977; 1978)	stimulus differences, passive	checkerboard, 2 shocks to digits, click	see ref.	.25/.25/.25/.25	1.5-2	Visual P300:S < C, D < C. Auditory P360:S < C. P300 normal in non-psychotic patients.
5. Roth et al. (1979)	oddball with/without warning, passive	2 tones, chord	65/80 dB SPL	.70/.20/.10	1	P300:S < C but not significant due to large SDs in S and C.
6. Roth et al. (1980a; 1980b)	A. oddball, RT	2 tones; one is target	85 dB SPL	.85/.15	1	P330:S < C; RT: S > C; Hits: S < C; RTSD S > C, but P330:S < C even when RTs matched.
	B. stimulus differences, passive	tone, noise	70/100 dB SPL	.25/.25/.25/.25	4	P300 to 100 dB noise:S < C.
7. Roth et al. (1981)	A. oddball, RT	2 tones; one is target	85 dB SPL	.85/.15	1	P350:S < D < C; RT:S > D = C Hits: S < D = C; RTSD: S > D > C
	B. oddball, RT	3 tones; one is target	85 dB SPL	.80/.10/.10	1	P350 for target or non-target infrequent:S < D < C. RT:S = C = D. Hits: S < D = C; RTSD: S > D = C.
	C. intensity differences, passive	noise	85/100/115 dB SPL	.33/.33/.33	4	P320 for 115 dB:S = D = C.
8. Pass et al. (1980)	oddball, RT; "Continuous Performance"	6 visual letters; one is target	?	.17 for each	1	P300:S < C; RT:S > C. Errors of commission and omission: S > C.

Table 1 - (continued)

9. Josiassen et al. (1981)	oddball, count	4 shocks to digits; one is target	2 mA > threshold	.25 for each	2.3-3.3	P400: Patients < C. (Most patients were schizophrenics)
10. Steinhauer and Zubin (in press)	oddball, count	2 tones; one is target	65 dB SL	.75/.25 (see ref.)	3	P300:S < D < C. S < C even when only accurately counted blocks are considered. Pupillary dilation: S < C.
11. Friedman et al. (in press)	oddball, RT	2 tones, omitted tone; one is target	64 dB SPL	.66/.17/.17	0.8	P350 to target tone and P400 to missing tone: high risk children (10-18 yrs) < Control children.
12. Cohen et al. (1981)	oddball, count	2 clicks, click + light: one is target	70/50 dB SL	.80/.10/.10	1.65	P340: S < C = Alcoholics. P340 correlates with accuracy. No relation between SCR responsivity and P340.
13. Baribeau-Braun et al. (in preparation)	dichotic listening, RT	3 tones in two ears; one is target	65 dB SPL	.45/.05	.25-.75/ .50-1.50	P300: S < C even for trials with RT accurate and < 500 msec.
14. Duncan-Johnson et al. (in preparation, a)	choice RT, sequential effects	2 tones; both are targets	85 dB SPL	.50/.50	1.5	P300:S < C though for P300 sequential effect: S = C. RT: S > C.
15. Duncan-Johnson et al. (in preparation, b)	simple RT, modality shift effects	tone, light; both are targets	40 dB SL (tone and light)	.50/.50	1.5-3.5	P300: S = C whether modality shifts or not. RT:S = C.

variables that control P300 amplitude and latency (for reviews, *see* Pritchard 1981, and Donchin 1981). When the findings are put in perspective, astonishingly close empirical and theoretical parallels can be drawn between P300 and SCR. The categories under which these similarities can be enumerated are listed in Table 2. Both P300 and SCR can be elicited by stimuli of diverse types, both are enhanced by various kinds of stimulus surprise, task relevance, and salience, and both show habituation. Neuronal and probabilistic models developed by Sokolov and others apply equally well to both responses. Cognitive and computer models of stimulus evaluation and context updating developed for P300 by Donchin and his students are being applied to SCR. A detailed documentation of these parallels can be found by Roth (in press-b).

Table 2

Parallels Between P300 and SCR

I. Empirical Parallels
- A. Stimulus Nonspecificity
- B. Stimulus Properties Controlling P300 and SCR Amplitude
  - 1. Surprise
    - a. Occurrence uncertainty
    - b. Stimulus quality deviation
    - c. Temporal uncertainty
    - d. Temporal deviation
  - 2. Task Relevance
    - a. Signal value
    - b. Allotment of attentional resources
  - 3. Salience
- C. Habituation

II. Theoretical Parallels: P300 and the OR
- A. Neuronal Models
- B. Probabilistic Models
- C. Cognitive Models
- D. Computer Models

In a psychological sense, both SCR nonresponding and P300 reduction imply an inability to mobilize extra stimulus processing resources when the novelty or other features of the stimuli warn that additional resources may be required momentarily. These extra resources may actually turn out to be unnecessary, in that RT or counting tasks of a simple nature can be performed adequately with the available resources even when the stimulus comes as a surprise. The differences between psychotics and controls in mobilizing these resources may be apparent only at intermediate levels of stimulus novelty or task demand. When stimuli are expected and uninteresting, neither group responds; when stimuli are very novel, task-relevant, or intense, both groups may respond equally.

In a biological sense, SCR nonresponsivity and P300 reduction imply a failure of components of the orienting reflex. This innate basic mechanism for reacting to potentially dangerous stimuli in the environment is found in both vertebrates and invertebrates (e.g., Kandel 1981).

Our unitary interpretation of SCR and P300 could be challenged on the basis of the results of Cohen et al. (1981). Their study is up to now the only one to report SCR and ERP measures in the same patients, although from different paradigms. As usual, about half of the schizophrenics were SCR nonresponders in a habituation paradigm, but both SCR responders and nonresponders had reduced P300s in an oddball paradigm. Either their P300 paradigm was more sensitive than their SCR paradigm to a general schizophrenic deficit that differs quantitatively among schizophrenics, or their SCR paradigm differentiated subgroups of schizophrenics that differ qualitatively from each other. Although SCR and P300 are generally under the control of the same independent variables, it is possible that they reflect distinct and dissociable information processing mechanisms (*see* Roth, in press-b).

Since it has been suggested that there are at least two biologically distinct types of schizophrenics, one suffering from dopaminergic hyperactivity and the other from enlarged cerebral ventricles (Crow 1982), it is tempting to try to assign SCR nonresponders to one of these types. However, definite assignment of SCR or P300 abnormalities to specific subtypes of mental disease must await systematic investigations in which patients are studied from multiple perspectives simultaneously. Nonresponsivity should be assessed in various physiological systems from the brain to the periphery, and these data should be compared with biochemical, radiological, psychological, linguistic, and clinical-historical data. Converging findings may help us discover groups of patients with diseases of distinct etiologies and prognoses.

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What Is Vital Depression (Endogenous Depression or Melacholia), and How Can It Be Reliably Assessed

Chair: Robert M.A. Hirschfeld, M.D.
Clinical Research Branch
National Institute of Mental Health
Rockville, Maryland

Pituitary-Adrenal Assessment in Identifying Subtypes of Depression

Walter Armin Brown, M.D.,[1] and C. Brandon Qualls, M.D.[2]

About 50 percent of patients with primary major depressive disorder show pituitary-adrenal disinhibition while they are depressed but not after recovery. This endocrine phenomenon provides a model for examining the value of a biological marker in subtyping depressive illness.

The dexamethasone suppression test (DST), because of its procedural simplicity, lack of risk, minimal discomfort to the patient, relative ease with which normal and abnormal responses are differentiated, and demonstrated clinical correlates has been the method most widely applied for assessing pituitary-adrenal activity in studies of psychiatric patients. Recent studies using the DST in depressed patients have examined the clinical correlates of normal and disinhibited pituitary-adrenal activity. With respect to existing diagnostic categories, Brown and Shuey (1980) and others (Schlesser et al. 1980) have found that nonsuppression after dexamethasone occurs almost exclusively in patients with primary major depressive disorder; very few patients with secondary depression (those with a preceding psychiatric diagnosis other than affective) show nonsuppression. Carroll and his associates (Carroll et al. 1981) have reported that nonsuppression occurs exclusively in patients with endogenous depression or melancholia; patients with nonendogenous depression showing normal suppression. Yet whether one examines patients who meet criteria for melancholia, primary depression, or endogenous depression, one finding has been consistent from study to study: Patients in each of these diagnostic categories are heterogenous in their pituitary-adrenal activity. Depending on the DST protocol, 30 to 65 percent are nonsuppressors and the remainder suppressors. This heterogeneity has focused the authors' attention on dimensions of depressive illness other than diagnosis that might correlate with pituitary-adrenal activity.

Although in a few studies (Davis et al. 1981) nonsuppressors have been observed, on the basis of rating scale scores, to have a more severe depression than suppressors, this is not a consistent finding (Brown & Qualls 1981). A few patients who have been nonsuppressors during one major depressive episode have been studied during subsequent periods of depression. Nonsuppression has occurred in these patients only in the context of severe depressive symptomatology, not with minor or transient depression (Brown & Qualls, unpublished observations). Thus there may be a severity threshold for nonsuppression.

[1]Department of Psychiatry, Providence Veterans Administration Medical Center and Brown University, Providence, RI 02908.
[2]Department of Psychiatry, Brown University and Butler Hospital, Providence, RI 02908.

However, since many suppressors have, by any criteria, a severe illness, the differences in pituitary-adrenal activity among depressed patients are not likely to be accounted for by differences in severity of illness.

Nor do suppressors and nonsuppressors differ consistently in the occurrence or intensity of suicidal ideation, agitation, anorexia, sleep disturbance, or other specific depressive symptoms. Yet one symptom dimension in depressed patients—cognitive impairment—does appear to consistently correlate with pituitary-adrenal activity. Nonsuppressors have more difficulty than suppressors in completing self-rating scales (Brown & Shuey 1980), have longer reaction times (Brown & Qualls 1981), are rated as having greater thinking disturbance (Reus 1982), and make more errors of commission on a recognition task (Reus, unpublished observations). Further, a significant positive correlation has been observed between urinary cortisol and number of errors on the Halstead Categories Test (Rubinow, unpublished observations). In summary, the studies to date have consistently shown that depressed patients with pituitary-adrenal disinhibition have a greater degree of cognitive impairment than those with normal pituitary-adrenal regulation.

Nonsuppressors have been found to differ from suppressors on three dimensions of illness course: they are older at both the index episode and their first depressive episode (this age difference appears to be sex related; it occurs most clearly in depressed women); irrespective of treatment, nonsuppressors seem to undergo greater improvement during hospitalization (Brown & Qualls 1981; Greden et al. 1980); and, retrospective studies show that nonsuppressors have more episodes of depression (Brown & Qualls 1981; Schlesser et al. 1980).

A few studies, all of which must be considered preliminary, suggest that nonsuppressors and suppressors differ in their response to specific treatment. Whereas nonsuppressors appear to respond well to desipramine and imipramine (Brown & Qualls 1981; Greden et al. 1981), they show a poor response to clomipramine (Brown et al. 1980) and mianserin (Cobbin et al. 1981). Suppressors, on the other hand, seem to respond equally well to these antidepressants. Clearly, more data are needed to definitively answer the question of whether suppressors and nonsuppressors respond preferentially to different antidepressants. The little data available so far lend themselves to the interpretation that nonsuppressors respond better to drugs having their predominant effects on noradrenergic rather than serotonergic systems. This preferential drug response would be consistent with the known serotonergic excitatory and noradrenergic inhibitory input to pituitary-adrenal regulation.

Suppressors and nonsuppressors appear to differ in their response to electroconvulsive therapy (ECT). The authors have found that of 13 suppressors and 12 nonsuppressors treated with ECT clinical improvement occurred in all of the suppressors but in only six (50%) of the nonsuppressors. Six nonsuppressors did not respond to ECT according to both rating scale criteria and their clinician's impressions. These observations are consistent with those of Papakostas et al. (1981) who, although not directly addressing the predictability of the DST for ECT response, reported that 5 of 14 nonsuppressors treated with ECT did not improve, a higher than usual rate of nonresponse.

Suppressors and nonsuppressors differ in their responses to methylphenidate and sleep deprivation, treatments which induce in some patients a transient relief of depressive symptoms. Significantly more suppressors than nonsuppressors show an antidepressant response to methylphenidate (Sternbach et al. 1981), but more nonsuppressors than suppressors respond to sleep deprivation (Nasrallah & Coryell 1982).

The apparent differences between suppressors and nonsuppressors in course of illness and response to specific treatments suggest that the depressive illnesses associated with normal and abnormal pituitary-adrenal regulation differ in their pathophysiology. Two other bits of data support this concept. Schlesser and his associates (1980) reported that nonsuppressors are more likely to have a family history of depression than suppressors; and, the authors have found (1982) that people are consistently suppressors or nonsuppressors over multiple depressive episodes. These observations suggest that the depression associated with pituitary-adrenal disinhibition may, more so than other depressive illnesses, have a genetic component and, consistent with this, there may be stable individual differences in the propensity to develop pituitary-adrenal

disinhibition with depression. Thus pituitary-adrenal assessment may identify a subtype of depression having a distinct pathophysiology with characteristic clinical and treatment response features.

Diagnostic categories based on symptomatic phenomenologic criteria rarely identify illnesses which are homogeneous with respect to etiology, pathophysiology, or treatment requirements. Many illnesses that differ little if at all symptomatically have differing underlying pathophysiologies that are critical in determining effective treatment and prognosis. Pneumonia, hypertension, and probably depression as well, are among them. On the other hand, as with vitamin deficiencies, porphyria, and syphilis, a single pathophysiologic process which must be identified for effective treatment, can have differing symptomatic presentations. Pituitary-adrenal disinhibition may be associated with a psychiatric illness having a number of symptomatic presentations, depression perhaps the most common. Such an illness might respond, however, to one or more specific treatments. One study has shown that among patients with mixed psychiatric diagnoses including catatonia, schizoaffective disorder depressed, and paranoid schizophrenia, nonsuppressors regardless of "diagnosis" but not suppressors, respond to thymoleptic treatments—lithium, ECT, and secondary amine tricyclics (Carman et al. 1980).

Among depressed patients pituitary-adrenal disinhibition is associated with cognitive impairment, a tendency to recurrence, and an emerging profile of response to specific treatments. This neuroendocrine dysfunction and other neuroendocrine and neurochemical markers may help reorient our thinking about the dimensions of psychiatric illness relevant to "diagnosis" and provide a stepping stone to a classification of depression more closely tied to pathophysiology and treatment than current phenomenologic approaches.

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Benzodiazepine Abuse: What Are the Data?

Chair: Charles P. O'Brien, M.D., Ph.D.
University of Pennsylvania
VA Medical Center
Philadelphia, Pennsylvania

Subjective Effects of Benzodiazepines and Methaqualone in Recreational Sedative Users

Jonathan O. Cole, M.D.,[1] Maressa Hecht Orzack, Ph.D.,[1] Francine M. Benes, M.D., Ph.D.,[1] Barbara J. Beake, A.B.,[1] Michael P. Bird, A.B.,[1] Yoram Bar Tel, M.A.,[1] and Martin Ionescu-Pioggia, A.B.[1]

Sedative drugs, including methaqualone and various barbiturates, are generally agreed to have abuse potential and are used recreationally as "street" drugs. Some individuals become physically and psychologically dependent on these agents. Recreational use of benzodiazepines is less well documented, though some reports exist, and physical dependence is believed to be relatively uncommon. Nevertheless, a number of cases of physical dependence have been documented in the world literature.

If one assumes that the relative abuse liabilities of various benzodiazepines are unclear, one feasible approach to documenting their abuse liabilities would be to compare them, first, to each other and, second, to a sedative drug of known abuse potential such as methaqualone. Our group is currently engaged in a program of studies which is working toward this objective. The present paper should be viewed as a progress report on work completed to date. Two studies, one comparing methaqualone in single doses of 200 mg and 400 mg with placebo and a second comparing 20 mg of prazepam with 10 mg of diazepam and placebo, have been completed. Studies directly comparing a higher dose of diazepam (20 mg) with higher doses of prazepam (40 mg) and with methaqualone are now in progress.

Methaqualone had been selected as a "standard" abuse-liable sedative because of its popularity with recreational sedative users in the Boston area. It is a chemically synthesized molecule which belongs to a group of compounds called the oxoquinazolines. As such, it is structurally similar to piperidone and barbiturate hypnotic drugs (Brown & Goenechea 1974). Methaqualone is absorbed rapidly after oral administration (Meyer & Boggan 1977) and, in man, average peak plasma levels occur at 2 hours after administration (Morris et al. 1972). Unbound plasma methaqualone is free to diffuse passively into the cerebrospinal fluid compartment in proportion to its concentration (Christensen & Holfort 1975). The primary route of metabolism of the drug is through the hepatic microsomal mixed oxidase enzymes (Prabhu et al. 1964). SKF 525-A, a compound which inhibits the liver metabolism of methaqualone, enhances its distribution into various subcellular compartments within the brain, including cytoplasm, myelin, and, to a much lesser degree, synaptosomes, mitochondria, and microsomes (Kuhn & Shah 1978). Within 8 hours of oral administration, 80-90 percent of the drug present in plasma has been cleared (Morris et al. 1972), the principal route or excretion for methaqualone and its metabolites being through the urine. In human subjects, its rate of elimination is quite variable,

[1]Psychopharmacology Program, McLean Hospital-Harvard Medical School, Belmont, MA 02178.

and the estimated half-life of methaqualone in urine can be as long as 74 hours (Heck et al. 1978).

Methaqualone is a short-acting anesthetic and muscle relaxant which in man produces slow wave changes in the electroencephalogram (EEG) similar to those observed with barbiturates (Saxena et al. 1977). The ability of methaqualone to reduce seizure susceptibility in mice (Boggan et al. 1977) appears to be associated with enhancement of transmission at GABA-nergic synapses in the central nervous system (Naik et al. 1978). Although methaqualone is a potent inhibitor of specific ^{3}H-diazepam binding to rat brain synaptosomal membranes (Muller et al. 1978), its central depressant effects do not appear to be mediated through a direct action of GABA receptors (Naik et al. 1978). As a lipophilic substance which has been demonstrated in various brain compartments, the range of possibilities to account for its various actions is very broad and its interaction with GABA-nergic neurons may be only one of many possible mechanisms of action in the central nervous system.

In addition to its clinically useful physiological effects, methaqualone has euphoriant, relaxant, and anxiolytic properties which have been associated with its recent widespread nonmedical use (Gerald & Schwirian 1973). Individuals who take methaqualone consistently report its preferred use in social settings (Gerald & Schwirian 1973; Kochansky et al. 1975), and its apparent aphrodisiac properties appear to be among its most desirable effects (Gerald & Schwirian 1973). Studies of methaqualone effects in monkeys have demonstrated an increase of "affiliative activities" including grooming, huddling, and sitting together, although curiously, sexual functions while under the influence of the drugs were primarily autoerotic (Claus et al. 1980).

The accumulated experience with nonmedical use of methaqualone has revealed that a variety of complications can arise. Interference with memory recall and stimulus discriminability (Rundell et al. 1975), tolerance (Faulkner et al. 1979), physical dependence (Singh et al. 1980), abstinence syndromes with potentially life-threatening seizures (Swartzburg et al. 1973), and peripheral neuropathy (Mark & Sloggem 1976) are among the more serious complications of long-term methaqualone abuse. In addition, methaqualone-diphenhydramine (Mandrax®), a commercially produced combination drug, has also been associated with dose-related psychotic reactions, intoxication-related suicide attempts, and violent episodes (Tennant 1973).

Despite its potential complications, methaqualone is a sedative hypnotic with considerable abuse potential which appears to derive from its recreationally desirable effects. As such, it represents a useful investigative tool to explore the effects of such agents on individuals and their social interactions under controlled laboratory conditions. Such a controlled laboratory setting employing standardized assessment batteries, once established, could later be applied to the study of other sedative hypnotic drugs to determine their respective abuse liability relative to methaqualone as a reference standard. Methaqualone has been evaluated for subjective and physiological effects by Jasinski et al. (1977) and found generally comparable to pentobarbital in its subjective effects.

The prazepam-diazepam comparison was undertaken on the presumption that diazepam's relatively rapid absorption, which gives peak blood levels 30-90 minutes after oral ingestion (Bliding 1974), might make it more subjectively reinforcing than prazepam which is converted into desmethyldiazepam in the body and gives peak plasma levels of this compound only at about 6 hours (Chang et al. 1978). In our clinical experience patients often feel more rapid relief from anxiety on diazepam than on other benzodiazepines. The doses were selected as representing high standard clinical dosage units (Woody et al. 1975). Higher dosages are often selected for recreational purposes, but lower dosages were chosen to work out a useful methodology before higher levels were studied.

The designs for both studies were essentially identical. Subjects were recruited by notices posted in various local colleges. Most were students from socio-economically upper middle or upper class families who were college educated. All participants were casual users of sedative-hypnotics, such as barbiturates, methaqualone, and benzodiazepines, and had used one or more of these drugs at least six times in doses above the usual prescribed levels. Subjects were required to complete the Minnesota Multiphasic Personality Inventory (MMPI) (Dahlstrom et al. 1972) and undergo a clinical interview. The latter was conducted by a clinical psychologist who determined

previous drug usage, probed for areas of personality dysfunction and adverse reactions to stress, and reviewed the psychiatric history of the subject and his family of origin. Results from both the MMPI and the clinical interview were used as criteria on which to judge the subjects' suitability for participation. The mean MMPI profile of male and female subjects showed elevations of scales 4 (Pd – psychopathic deviate) and 9 (Ma – mania), but these were below a T-score of 70. This pattern is characteristic of a hypomanic and sociopathic personality style that is generally within the range of normal behavior (Dahlstrom et al. 1972). In addition, subjects had a normal physical examination, no history of drug dependence including alcohol, and had no unusual side effects during their previous drug experiences.

Separate groups of 24 subjects, 12 male and 12 female, were recruited for the methaqualone and the diazepam-prazepam studies. Four subgroups of six subjects each, two male subgroups and two female subgroups, were created.

Measures

The major dependent measure for the present report was List 116 of the Addiction Research Center Inventory (ARCI), a 102-item inventory which characterizes the subjective effects of a drug compared with those of other well-known drugs of abuse (Haertzen 1974). This version contains seven standard scales in addition to an 11-item Amphetamine scale developed by Martin et al. (1971) plus Euphoria and Sedation scales established by Jasinski et al. (1977). The utility of these scales in investigating the subjective effects of various substances is well documented (Martin et al. 1971; Jasinski 1977; Jasinski et al. 1977).

Although the ARCI was originally a true/false questionnaire, we devised two variants for use in these studies. For the methaqualone study, a 7-point version was used; subjects were asked to rate themselves on intensity from 0 to 6. For the prazepam study, a 10-point version was used; subjects were asked to rate themselves on each item from −5 to +5. The same scales were used in both studies, but the actual numerical scores obtained on the scales are not strictly comparable across studies. Different versions of the Profile of Mood States (POMS) (McNair et al. 1971) were used in the two studies; neither version seemed as sensitive to drug-placebo differences as the ARCI. The POMS results will not be presented at this time.

Testing Procedures

Subjects were run in groups of six, with each group coming in for three 5-hour sessions, 1 week apart. Each subject in fact received all three treatments (20 mg of prazepam, 10 mg of diazepam and placebo, or 400 mg and 200 mg of methaqualone and placebo) in random order and double-blind. Thus, each subject served as his or her own control for the experiment. Randomization of treatments ensured that only two subjects in each group were receiving the same drug during each session. Subjects themselves were not aware that they would receive a different treatment at each session, and only knew the possible treatments they *could* receive.

Subjects were instructed to abstain from drug usage for 72 hours and alcohol for 12 hours prior to each session; they were asked to give a urine sample at the beginning of the session to be screened for illicit drug usage that might interfere with the validity of their ratings. No illicit use was detected. Initial physiological measures including pulse, temperature, and blood pressure were obtained. Pulse determinations were repeated hourly, while blood pressures were obtained only at the beginning and the end of each session.

The POMS and ARCI self-rating questionnaires were administered at the outset (predrug) and then hourly for 4 (methaqualone) or 5 (prazepam) hours following drug ingestion. Subjects were also asked to guess which drug they thought they and the other subjects received, what rate they would pay for what they had received, and how high they felt during the session.

Groups were run in a living-room-like atmosphere in which subjects were free to play games, talk, read, listen to music, and eat, starting 1 hour after drug ingestion during the times when they were not filling out ratings. Each rating took about 25 minutes, leaving the subjects a substantial amount of free time.

Table 1

Covariance F-Ratios of ARCI Scores: Methaqualone Study

Scale	Drug	Time	Sex	Drug-Time	Time-Sex	Drug-Sex
Amphetamine	16.90**	37.25**	4.72*	7.27**	1.98	0.34
Drunkenness	31.66**	26.42**	5.83*	12.83**	1.85	1.35
Excitement	5.32**	35.45**	7.67**	7.37**	0.34	0.02
LSD	13.64**	27.68**	1.12	4.81**	2.77*	1.01
MG	4.77**	14.34**	1.39	3.00**	0.07	0.06
MPG	12.35**	54.31**	5.93**	8.66**	1.05	0.01
PCAG	11.03**	2.96*	0.19	3.06**	2.04	1.78
Sedation	15.47**	0.86	1.09	3.61**	2.33	1.17
Euphoria	9.58**	41.41**	2.40	7.42**	1.12	1.26

* Significant at .05 level (two-tailed)
** Significant at .01 level (two-tailed)

Table 2

Covariance F-Ratios of ARCI Scores: Prazepam Study

Scale	Drug	Time	Sex	Drug-Time	Time-Sex	Drug-Sex
Amphetamine	1.36	30.27**	0.79	1.87	0.56	2.37
Drunkenness	4.00*	21.78**	1.88	4.22**	0.14	0.68
Euphoria	1.24	31.97**	0.15	2.88**	4.55**	0.41
Excitement	2.53	2.78*	2.37	1.57	0.58	1.09
LSD	4.12*	7.30**	0.73	0.78	0.43	0.58
MG	0.01	2.49*	4.71*	2.06*	1.31	1.04
MBG	1.32	19.50**	0.35	2.29*	1.80	1.46
PCAG	1.63	3.12*	7.37**	2.61**	0.13	0.26
Sedation	2.88	4.00**	6.50*	2.98**	0.26	0.27

* Significant at .05 level (two-tailed)
** Significant at .01 level (two-tailed)

Data Analysis

The F values and corresponding probabilities for main drug effects, time effects, sex effects, and interaction among these variables were obtained by an analysis of covariance (grouped by sex) which adjusted for variations in the subjects' predrug ratings. The baseline scores (predrug) depicted in the figures represent raw means for each scale, while postdrug scale scores have been covaried. No significant differences between the three treatment groups were observed on baseline ratings in either study. Results of this analysis for the ARCI are presented in Table 1 for the methaqualone study and in Table 2 for the prazepam study. Where main drug effects, drug-by-time interactions, or trends were observed, an analysis of variance of adjusted mean scores was performed for each separate time point on that measure. Differences between drug conditions at these time points were analyzed using a Neuman-Keuls multiple comparison statistic.

Results

Within both studies in the major analysis of covariance, main drug effects and drug-by-time interactions significant at the $p < .05$ level were taken as clear evidence of drug treatment differences. Significant main drug effects occurred when, by inspection, level differences between treatments, usually drug and placebo, were evident throughout the entire study period, while

drug-by-time interactions were statistically significant when drug-placebo differences were marked at one or two time periods, usually 1 and/or 2 hours after drug ingestion and then dwindled as the study period continued.

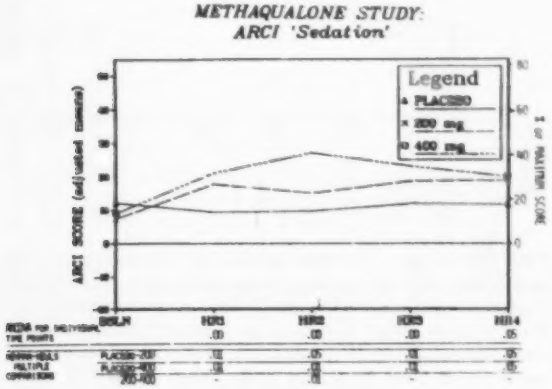

FIGURE 1. Drug vs. time curves for the comparison of orally administered methaqualone. Each point represents the mean ARCI scale score of each treatment at the five time levels (baseline to 4 hours post), adjusted from the analysis of covariance. Percent of maximum score is derived from the scale range (0-66): (mean score/scale range) x 100. Below the plot are displayed the results of the post hoc drug by time ANCOVA at each time point, and the Neuman-Keuls contrasts indicating drug-placebo/drug-drug differences.

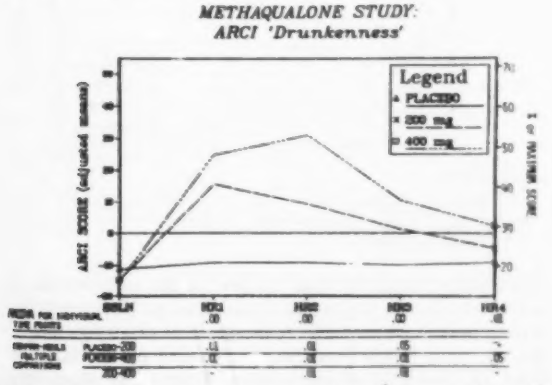

FIGURE 2. Drug vs. time curves for the comparison of orally administered methaqualone. Each point represents the mean ARCI scale score of each treatment at the five time levels (baseline to 4 hours post), adjusted from the analysis of covariance. Percent of maximum score is derived from the scale range (-30-96): (mean score/scale range) x 100. Below the plot are displayed the results of the post hoc drug by time ANCOVA at each time point, and the Neuman-Keuls contrasts indicating drug-placebo/drug-drug differences.

Treatment differences in the methaqualone study were highly significant by analysis of covariance (Table 1) at the $p < .001$ level for drug or drug-by-time or both on seven of the eight ARCI scales presented. The morphine group (MG) scale, designed to pick up characteristic effects of opiates, reached significance at the $p < .01$ level. Several of the measures, Sedation (Figure 1), Drunkenness (Figure 2) and PCAG (a scale to detect effects of pentobarbital, chlorpromazine, and alcohol group drugs) are measures of sedation or sedative-type intoxication. These scales did discriminate between 200 mg and 400 mg of methaqualone at the second and sometimes the third hour, showing the higher dose to be more sedative than the lower dose of methaqualone. On the Euphoria (Figure 3), Excitement, Amphetamine (Figure 4), and morphine-benzedrine group (MBG) scales, the two dosages of methaqualone were almost identical in the course and degree of drug effect with maximum effect occurring at 1 hour after drug ingestion.

In the prazepam-diazepam-placebo study (Table 2), main drug effects were less striking and drug-by-time interactions were more common, while significance levels were more modest than those seen in the methaqualone study. Sedative effects as measured by the Sedation (Figure 5),

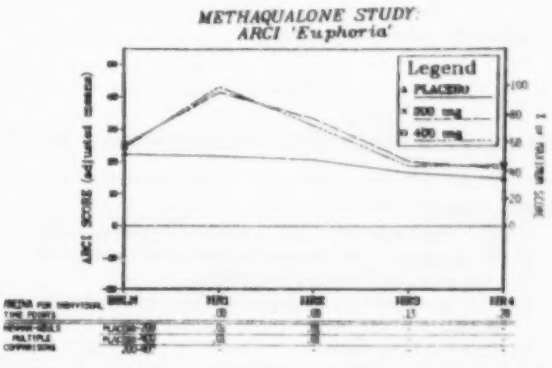

FIGURE 3. Drug vs. time curves for the comparison of orally administered methaqualone. Each point represents the mean ARCI scale score of each treatment at the five time levels (baseline to 4 hours post), adjusted from the analysis of covariance. Percent of maximum score is derived from the scale range (0-42): (mean score/scale range) x 100. Below the plot are displayed the results of the post hoc drug by time ANCOVA at each time point, and the Neuman-Keuls contrasts indicating drug-placebo/drug-drug differences.

Drunkenness (Figure 6), and PCAG scales were clearly significant. The sedation produced by both prazepam and diazepam in fact appeared equivalent to the 400 mg dose of methaqualone, while the degree of drunkenness produced by these agents was only comparable to the 200 mg dose range. Euphoriant effects were seen only on the Euphoria (Figure 7) and MBG scales, while a dysphoric effect was detected by the LSD scale.

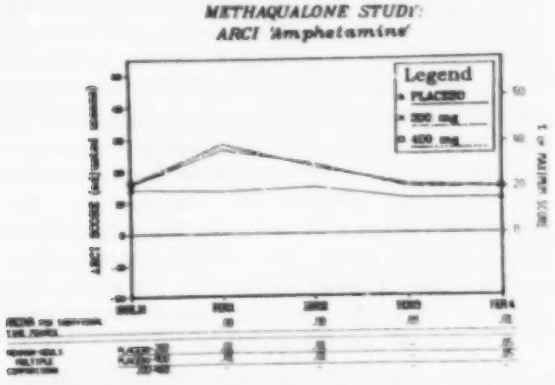

FIGURE 4. Drug vs. time curves for the comparison of orally administered methaqualone. Each point represents the mean ARCI scale score of each treatment at the five time levels (baseline to 4 hours post), adjusted from the analysis of covariance. Percent of maximum score is derived from the scale range (0-72): (mean score/scale range) x 100. Below the plot are displayed the results of the post hoc drug by time ANCOVA at each time point, and the Neuman-Keuls contrasts indicating drug-placebo/drug-drug differences.

Table 3

Items Contained in ARCI 'Abuse Potential' Scale

Positive Items:

1) My movements are free, relaxed, and pleasurable.
2) Things around me seem more pleasing than usual.
3) I am sure I will sleep well tonight.
4) I feel as if something pleasant had just happened to me.
5) My head feels light.
6) I feel a very pleasant emptiness.

Negative Items:

1) My face feels hot.
2) I feel as if I have the flu.
3) I feel like avoiding people, although I usually do not feel this way.
4) I have been getting cramps.
5) I have a feeling of just dragging along rather than coasting.
6) My head feels as it does during a hangover.

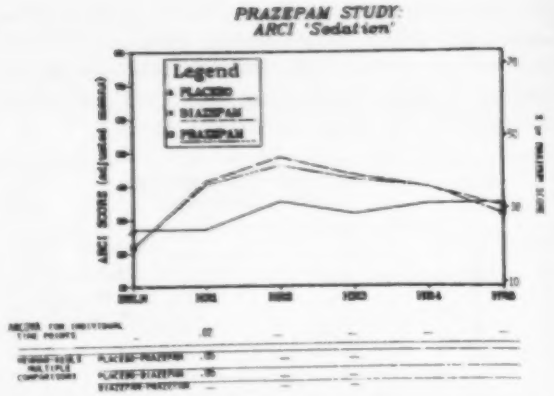

FIGURE 5. Drug vs. time curves for the comparison of orally administered prazepam and diazepam. Each point represents the mean ARCI scale score of each treatment at the six time levels (baseline to 5 hours post), adjusted from the analysis of covariance. Percent of maximum score is derived from the scale range (0-110): (mean score/scale range) x 100. Below the plot are displayed the results of the post hoc drug by time ANCOVA at each time point, and the Neuman-Keuls contrasts indicating drug-placebo/drug-drug differences.

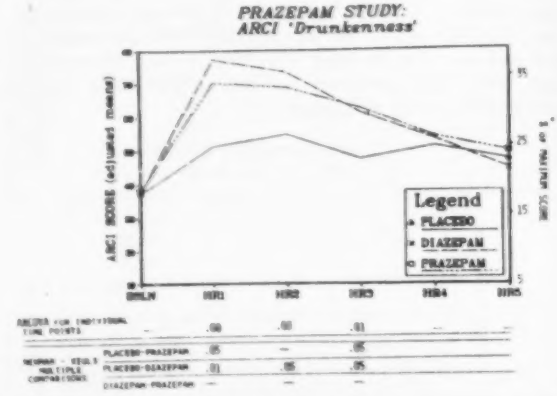

FIGURE 6. Drug vs. time curves for the comparison of orally administered prazepam and diazepam. Each point represents the mean ARCI scale score of each treatment at the six time levels (baseline to 5 hours post), adjusted from the analysis of covariance. Percent of maximum score is derived from the scale range (0-210): (mean score/scale range) x 100. Below the plot are displayed the results of the post hoc drug by time ANCOVA at each time point, and the Neuman-Keuls contrasts indicating drug-placebo/drug-drug differences.

By Neuman-Keuls analysis, diazepam-placebo differences were seen at more time points on the sedative scales than were prazepam-placebo differences, suggesting a tendency toward a more sedative effect for 10 mg of diazepam than for 20 mg of prazepam. No Neuman-Keuls contrasts were significant on the Euphoria scale for either drug though diazepam, by inspection, appears to be a bit more euphoriant. On the Excitation scale (Figure 8), an unexpected significance level of $p = .05$ showing diazepam to be more "exciting" than prazepam at 1 hour was uncovered, but its statistical meaningfulness is reduced by the main analysis of covariance significance level (a $p = .09$ main drug effect).

We have created an artificial "Abuse Potential" scale from the ARCI based on items correlating with the price the subject would have paid for the drug dose he received at any given study session. These items are listed in Table 3. The correlations

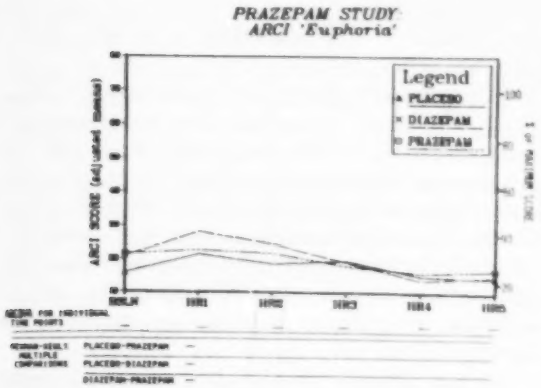

FIGURE 7. Drug vs. time curves for the comparison of orally administered prazepam and diazepam. Each point represents the mean ARCI scale score of each treatment at the six time levels (baseline to 5 hours post), adjusted from the analysis of covariance. Percent of maximum score is derived from the scale range (0-70): (mean score/scale range) x 100. Below the plot are displayed the results of the post hoc drug by time ANCOVA at each time point, and the Neuman-Keuls contrasts indicating drug-placebo/drug-drug differences.

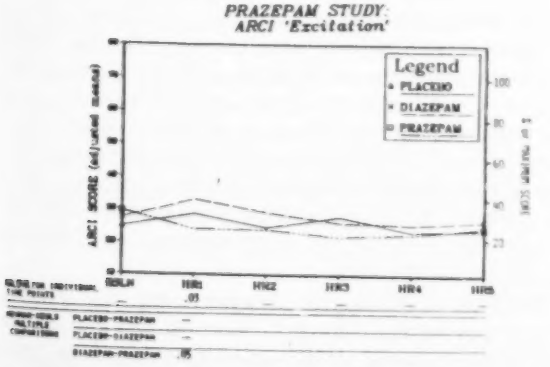

FIGURE 8. Drug vs. time curves for the comparison of orally administered prazepam and diazepam. Each point represents the mean ARCI scale score of each treatment at the six time levels (baseline to 5 hours post), adjusted from the analysis of covariance. Percent of maximum score is derived from the scale range (0-70): (mean score/scale range) x 100. Below the plot are displayed the results of the post hoc drug by time ANCOVA at each time point, and the Neuman-Keuls contrasts indicating drug-placebo/drug-drug differences.

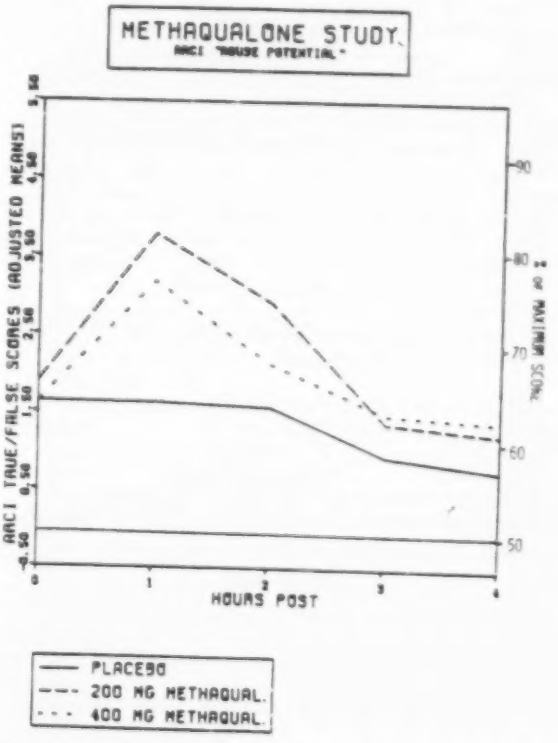

FIGURE 9. Drug vs. time curves for the comparison of orally administered methaqualone. Each point represents the mean ARCI "Abuse Potential" score of each treatment at the five time levels (baseline to 4 hours post), adjusted from the analysis of covariance. Items were scored true/false to standardize values. Percent of maximum score is derived from the scale range (-6-6): (mean score/scale range) x 100.

(which had to reach ± .32 for statistical significance) were obtained from combining data from the methaqualone study described above and from a similar 24-subject study comparing 15 mg and 30 mg of dextro-amphetamine with placebo. By scoring the "Abuse Potential" items in the ARCI used in both the methaqualone and prazepam-diazepam studies true-false, we have been able to create comparable graphs for the two studies showing adjusted means on this measure (Figures 9 and 10). This measure showed highly significant drug-placebo differences for methaqualone ($p = .004$) and also showed the lower 200 mg methaqualone dose to be "preferred" to the 400 mg dose. This phenomenon is probably a function of the higher euphoria to sedation ratio in the 200 mg dose. Drug-placebo differences in the prazepam-diazepam study, however, were not statistically significant. Despite this, a visible tendency for diazepam to look more "abuse liable" than prazepam at the dosages studied is apparent.

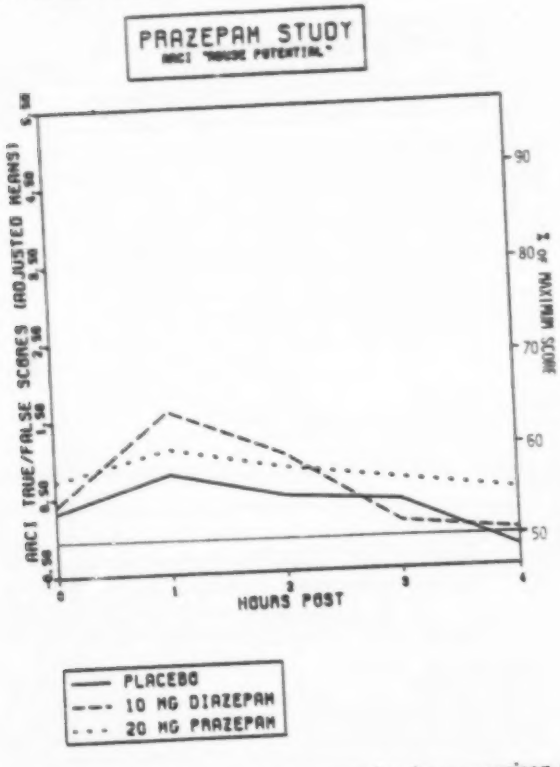

FIGURE 10. Drug vs. time curves for the comparison of orally administered prazepam and diazepam. Each point represents the mean ARCI "Abuse Potential" score of each treatment at the five time levels (baseline to 4 hours post), adjusted from the analysis of covariance. Items were scored true/false to standardize values. Percent of maximum score is derived from the scale range (-6-6): (mean score/scale range) x 100.

Discussion

The general approach to assessing the abuse liability of drugs described here, involving four groups of six subjects each selected for past experience in the recreational use of drugs in the class under study and the use of a reduced version of the ARCI as the main measure of subjective drug effects, is supported by the results obtained. Dose-effect results were obtained for methaqualone on sedative but not on euphoria-like measures.

Effects of the two benzodiazepines appear similar in direction but less in degree. Since only moderate clinical dosages were studied, the major questions about the abuse potential of benzodiazepines, as potentially measurable by our methodology, are not answerable. Very weak trends in the prazepam-diazepam data suggest that at higher doses of both drugs diazepam *might* be clearly more euphoriant. This possibility was strengthened by data presented by Jasinski (1981) in which a dose-response effect of both diazepam and chlordiazepoxide was obtained on the ARCI Sedation scale. Diazepam, but not chlordiazepoxide, showed dose-related increases on the ARCI Euphoria scale, suggesting that benzodiazepines may well differ among themselves in their euphoriant properties. A comparison of the effects of 20 mg of diazepam and 40 mg of prazepam in 12 recreational sedative users has just been completed. These data will be examined for differential effects of the two drug regimens on Euphoria and related scales.

The authors are also revising the scoring system for the ARCI. A factor analysis of 2-hour ARCI scores from our methaqualone and *d*-amphetamine studies has yielded three factors which measure euphoria, sedation, and dysphoria. These factors should provide clearer and, hopefully, more sensitive scales than the empirical ARCI scales we have been using. Jasinski et al. (1977) have used only the Sedation and Euphoria scales. Since PCAG and its subscale Sedation, and Drunkenness correlate between 0.76 and 0.96, while MBG and its subscale

Euphoria, Excitement, and Amphetamine correlate between 0.83 and 0.95, this limited assessment may be justified. The LSD scale, by contrast, seems to measure somatic and psychic dysphoria and correlates moderately well (0.46 to 0.70) with all other ARCI scales. It remains to be seen whether a new, factor analytic set of ARCI scales will be more sensitive or sensible than other approaches used to date.

The next difficult question is whether the system being used is a valid way of assessing the abuse liability of sedative drugs. It is unclear to what extent the benzodiazepines are actually abused, and the newer agents, such as prazepam, may not be abused at all. Illicit use probably reflects past and present popularity, as well as availability of the drugs. Methaqualone and diazepam are both known to illicit users, but prazepam may not be. After consideration of higher dose studies, the authors will be better able to assess the relative euphoriant and sedative qualities of benzodiazepines. If their methods do ultimately show methaqualone to have a higher euphoria/sedation ratio than diazepam, they will have more tangible data with which to characterize the abuse liability of the latter. Prazepam appears to be even less euphoriant than diazepam, and thus may be less liable to be abused. Illicit drug abuse as measured by epidemiologic surveys or law enforcement data may show a pattern of abuse popularity and/or frequency which reflects the trends observed in these studies. Unfortunately, good quality data on frequency of illicit use is lacking. At present, methods such as theirs are the most feasible approach to assessing the abuse potential of sedative drugs.

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What Is the Effect of "Stress" on Neuroendocrine Function? In-Depth Consideration of Recent Theorizing

Chair: **Redford B. Williams, Jr., M.D.**
Duke University Medical Center
Durham, North Carolina

Heterogeneity in the Response Pattern of Organ Systems to Stress: Mediators and Mechanisms

Cynthia M. Kuhn, Ph.D.,[1] Alberto Grignolo, Ph.D.[1] Mark Johnson,[1] and Saul M. Schanberg, M.D., Ph.D.[1]

Ornithine decarboxylase (ODC, E.C.4.1.1.17) catalyzes the first step in the synthesis of the polyamines putrescine, spermidine, and spermine. This enzyme is an extremely useful index of cellular response to stimulation because its activity changes rapidly in response to numerous physiological events that affect the metabolic activity of the cell. In this laboratory, ODC has been used as a tool to characterize the effects of a number of hormones and neuroeffectors on tissue function, and to identify mediators of stress effects in developing and adult rats. Previous studies have shown that pharmacologic or physiologic stimulation of the sympathetic nervous system (SNS) by alpha or beta adrenergic agonists, insulin-induced hypoglycemia, or other simuli increases ODC activity in several organs including heart, kidney, liver, and aorta (Thadani & Schanberg 1979; Slotkin 1979; Grignolo et al. 1982). In the present study, the pattern of tissue ODC response to stress and neural and nonneural mediators of stress effects have been investigated. These studies show that ODC responses to stress are determined by the organ, age of the animal, and the type of stress.

Two hours of continuous immobilization (IMM) increase ODC activity in liver, heart, kidney, and aorta. However, with longer periods of IMM, a more complex pattern is observed. ODC activity continues to increase in kidney and liver, while heart ODC decreases. In contrast,

[1]Department of Pharmacology, Duke University Medical Center, Durham, NC 27710.

shaker stress, which has been reported to cause sympathoadrenal activation and hypertension in experimental animals (Bunag et al. 1980), causes a marked decrease in heart ODC activity but no change in kidney or liver ODC activity (Table 1). Interestingly, these stresses evoke different patterns of ODC response despite the fact that both cause a marked increase in serum levels of corticosterone (Table 2). Corticosterone is a potent inducer of liver and kidney ODC activity (Panko & Kenny 1971; Nicholson et al. 1976), yet ODC activity increased during IMM but not shaker stress, despite significant elevations in serum corticosterone during both stress paradigms. These findings suggest that some other physiologic response associated with these stress paradigms contributes to the regulation of ODC activity.

Table 1

Effects of Shaker Stress on Tissue ODC Activity

Organ	Control		ODC Activity (percent control) 2 hours		6 hours	
Kidney	100 ± 19	(47)	113 ± 20	(11)	111 ± 19	(18)
Heart	100 ± 35	(48)	95 ± 15	(10)	32 ± 5*	(18)
Liver	100 ± 18	(40)	107 ± 16	(9)	71 ± 5	(19)

Animals were shaken in a group at 175 oscillations/minute for 2 or 6 hours or left undisturbed in the home cage, then killed and tissue ODC activity determined. Results are expressed as percent control ± SEM. *N* is indicated in parentheses.

* Indicates statistically different from control activity, $p < .05$ or better. Control ODC activity = 0.68 nmole/g/hr for heart, 4.99 nmole/g/hr for kidney, and 0.185 nmole/g/hr for liver.

Table 2

Effect of Shaker Stress and Immobilization on Serum Corticosterone Concentration

	Corticosterone (ng/ml)	
Control	45 ± 11	(13)
IMM	338 ± 74*	(15)
Shaker	267 ± 34*	(15)

Animals were left undisturbed (control), immobilized in wire mesh cages or shaken in a group (175 oscillations/minute) for 4 hours, then killed and serum corticosterone determined by radioimmunoassay. Results are expressed as ng/ml ± SEM.

* Indicates statistically different from control, $p < .001$. *N* is indicated in parentheses.

The fact that stimulation of the sympathetic innervation elevates ODC activity in several peripheral tissues (Thadani & Schanberg 1979, Slotkin 1979) suggested that stress effects might be mediated neurally. This possibility was investigated by determining the effect of the ganglionic blocker chlorisondamine on the ODC elevation associated with IMM. Chlorisondamine markedly inhibited the increase in heart ODC associated with IMM in 26-day-old rats (Table 4). These results suggest that the ODC increase after IMM is mediated primarily by neural mechanisms and helps explain the discrepancy between serum corticosterone levels and ODC activity that is observed during IMM and shaker. The finding that the ODC increase associated with IMM could be almost completely blocked by chlorisondamine indicates that the marked corticosterone elevation which occurs during IMM does not significantly stimulate ODC activity. This finding further suggests that tissue ODC sensitivity to glucocorticoid hormones is altered during stress. Suppression of GH sensitivity during stress has already been reported (Kuhn et al. 1979).

An effect of stress that cannot be explained by SNS activation is the decrease in heart ODC which is observed during shaker stress and after long periods of IMM. Findings from other laboratories suggest that certain stresses including prolonged IMM can increase *vagal* activity (Fitzgerald 1975). To investigate this possibility, animals were pretreated with atropine, and then exposed to shaker stress. Atropine did not affect basal ODC activity, but almost completely prevented the decline associated with shaker stress (heart ODC values in shaker animals = 30 ± 7% of control, while values in atropine-treated animals = 84 ± 12% of control). These results indicate that vagal activity contributes to the decline in ODC associated with shaker stress, and suggest that the decrease in heart ODC activity that occurs after 6 hours of IMM might also reflect increased vagal tone to the heart.

The ODC responses to stress described above are not constant throughout an animal's lifetime, but change as the animal develops. ODC responsivity to stress in immature animals differs from that observed in adults in two ways. First, certain environmental stimuli change ODC activity in neonates, but not in adults. Second, the changes

induced by classical stress paradigms are mediated by different physiological mechanisms in adults and neonates. Maternal deprivation (MD) of neonatal rats causes an immediate and long-lasting decline in ODC activity in most organs (Butler & Schanberg 1977). This decline is observed only in preweanling rats, and is initiated by the loss of a specific form of tactile stimulation of the pups by the mother (Butler & Schanberg 1977; Evoniuk et al. 1979). On the other hand, IMM or cold stress elevates ODC activity significantly in preweanling rat pups (Table 3). This finding suggests that maternal deprivation and the "classical" stress paradigms IMM and cold evoke distinct biochemical responses in developing rats. Furthermore, the heart ODC increase following IMM is not mediated neurally in pups, as chlorisondamine did not block stress effects in 10-day-old pups (Table 4). This finding is consistent with reports that functional sympathetic innervation of most peripheral organs is established between Days 12 and 16 postnatally (Slotkin 1979) and suggests that SNS activation is not the sole mediator of stress effects in developing animals.

These studies show that ODC responses to stress are a function of the type of stress, the organ, and the age of the animal. First, IMM and shaker evoke very different patterns of ODC response in adult rats, indicating that stress is not "nonspecific." Second, the sensitivity of a given organ to a hormone during stress appears to be modulated by concomitant changes in the activity of the autonomic nervous system and other endocrine systems. Furthermore, stress-induced secretion of certain hormones (e.g., corticosterone) does not necessarily lead to predictable biochemical responses in individual organs; that is, different tissue responses can be obtained in the presence of hormonal responses that are qualitatively and quantitatively identical. Third, certain stresses are effective only at certain maturational stages (e.g., maternal deprivation); others are effective at all ages but activate different effector pathways (e.g., neural vs. non-neural) depending upon the age of the animal and the maturity of those pathways.

Our studies of stress-induced changes in ODC activity suggest that this enzyme is an extremely useful tool for investigating hormonal and neural mediators of stress. By correlating ODC activi

Table 3

Effect on Stress on Tissue ODC Activity in Neonatal Rats

	Tissue ODC Activity (percent control)					
	Heart		Liver		Brain	
Control	100 ± 13	(35)	100 ± 24	(49)	100 ± 13	(14)
Maternal Deprivation	40 ± 9*	(57)	14 ± 4*	(48)	39 ± 3*	(15)
Deprived + Immobilized	101 ± 14**	(35)	98 ± 49**	(20)		
Deprived + Cold	151 ± 32**	(35)	140 ± 31**	(17)	70 ± 9**	(15)

Eight-day-old rat pups were deprived in an incubator, placed in an incubator in wire restraining cages, or placed in a 4° cold room for 2 hours. Controls were left with the mother for this time period. At the end of 2 hours, all animals were killed and tissue ODC activity was determined. Results are expressed as percent control ± SEM. *N* is indicated in parentheses.

*Indicates statistically different from control, $p < .05$ or better.

**Indicates statistically different from deprived animals, $p < .05$ or better.

Table 4

Effect of Chlorisondamine on ODC Activity During Immobilization

	ODC Activity (percent control)					
	Heart		Liver		Kidney	
Day 26						
Control	100 ± 13	(20)	100 ± 16	(18)	100 ± 17	(16)
Immobilized	297 ± 23*	(10)	277 ± 83*	(10)	1010 ± 300*	(9)
Chlorisondamine	85 ± 14	(20)	78 ± 16	(18)	162 ± 39*	(19)
Chlor + IMM	144 ± 21**	(10)	117 ± 11**	(10)	79 ± 20**	(10)
Day 10						
Control	100 ± 14	(8)				
Immobilized	171 ± 27*	(8)				
Chlorisondamine	108 ± 18*	(9)				
Chlor + IMM	200 ± 27*	(10)				

Animals were injected with saline or chlorisondamine, then immobilized for 2 hours in wire mesh cages and tissue ODC activity determined. Results are expressed as percent control ± SEM. *N* is indicated in parentheses.

*Indicates $p < .05$ or better relative to control.

**$p < .05$ or better relative to immobilized.

Control ODC activity = .295 nmole/g/hr for hearts on Day 26, 0.735 for Day 10, .238 nmole/g/hr for kidney and .399 nmole/g/hr for liver.

with endocrine and neural response patterns, we can obtain valuable information about the physiological responses of adult and immature animals to environmental challenges.

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Neurotransmitter Receptors: Heterogeneity, Regulation, and Function

Chair: Henry I. Yamamura, Ph.D.
Department of Pharmacology
University of Arizona Health Sciences Center
Tucson, Arizona

Correlation Between Pharmacological Activity and the Influence of GABA on the Binding of Flunitrazepam and the Specific Benzodiazepine Antagonist, Ro 15-1788[1]

Frederick J. Ehlert, Ph.D.,[2] William R. Roeske, M.D.,[2] Andrew Chen, B.S.,[2] and Henry I. Yamamura, Ph.D.[2]

Several lines of evidence indicate that gamma-aminobutyric acid (GABA) mechanisms are involved in the mediation of the pharmacological effects of benzodiazepines. The results of electrophysiological studies, for example, have shown that benzodiazepines potentiate the effects of GABA in a variety of neuronal systems (Tallman et al. 1980). Insight into the nature of the link between the pharmacological actions of benzodiazepines and GABA has come from biochemical experiments in which co-purification of GABA receptors and benzodiazepine receptors was demonstrated, and also from binding experiments in which GABA has been shown to enhance the binding of benzodiazepines (Olsen 1981). Results such as those described above have led to the suggestion that at least some benzodiazepine receptors are coupled to GABA receptor-chloride ionophore complexes. If the effects of GABA on the benzodiazepine receptor are related to the mechanism of action of benzodiazepines, then a correlation between the GABA modulation of binding and the pharmacological efficacy of a series of drugs which interact with the benzodiazepine receptor might be anticipated. Accordingly, we have found recently that GABA enhances the binding of the novel anxiolytic, CL218,872 (3-methyl-6-[3-trifluoromethylphenyl]-1,2,-4-triazolo[4,3-b]pyridazine) (Regan et al. 1981) but has little or no effect on the binding of presumptive pharmacological antagonist of benzodiazepines, propyl-carboline-3-carboxylate (Ehlert et al. 1981). Since a new class of compounds, the imidazodiazepines, have been reported to bind with high affinity to the benzodiazepine receptor and to antagonize selectively the pharmacological effects of tranquilizing benzodiazepines (Hunkeler et al. 1981), a quantitative study of the influence of GABA on the binding of the representative antagonist imidazodiazepine, Ro15-1788 (ethyl-8-fluoro-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate), might provide additional evidence for a correlation between GABA modulation of binding and pharmacological activity. In the present report, the results of

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[2]Departments of Pharmacology, Psychiatry, Biochemistry, and Internal Medicine and the Arizona Research Laboratories, University of Arizona Health Sciences Center, Tucson, AZ 85724.

such a study are presented and are shown to be consistent with the postulate that GABA enhances the benzodiazepine receptor binding activity of anxiolytics, like flunitrazepam (FLU), whereas the binding of benzodiazepine antagonists, like Ro15-1788, is largely insensitive to the influence of GABA.

Benzodiazepine receptor binding assays were carried out on the rat cerebral cortex using [^{3}H]FLU (83.6 Ci/mmole); the details of the assay have been given in a previous report (Ehlert et al. 1981). Briefly, cortical homogenates (20 mg original wet tissue weight/ml buffer) were washed five times by centrifugation and resuspension in fresh phosphate buffer (pH 7.4, 9.5 mM K^+, 81 mM Na^+, 50 mM PO_4). Binding was measured by the filtration method, and incubation lasted 30 min at 37°C.

Table

Effect of GABA on the Competitive Inhibition of [^{3}H]FLU Binding by FLU and Ro 15-1788

	IC_{50}[1]		IC_{50} control
	Control (nM)	10_{μ}M GABA (nM)	IC_{50} GABA
FLU (100 mM NaCl)	17.8	5.6[2]	3.2 (2.1 - 4.7)[3]
Ro15-1788	5.6	6.3	0.89 (0.64 - 1.2)
Ro15-1788 (100 mM NaCl)	7.1	6.3	1.1 (0.89 - 1.3)

[1]The IC_{50} represents the concentration of non-labeled drug that caused 50% inhibition of specific [^{3}H]FLU binding. Each IC_{50} value represents the geometric mean of values from four experiments.
[2]Significantly different from control, $p < 0.005$.
[3]95% confidence limits.

The results of FLU/[^{3}H]FLU and Ro15-1788/[^{3}H]FLU competition experiments carried out in the presence or absence of GABA (10^{-5} M) are shown in the Table. In the presence of 100 mM NaCl, GABA caused a 3.2-fold reduction in the IC_{50} of FLU from 17.8 nM in controls to 5.6 nM in the presence of GABA. Since the concentration of [^{3}H]FLU (0.5 nM) used in the competition experiment was much less than the IC_{50} values, correction from IC_{50} to K_i led to negligible changes in the results. We have shown previously that in the absence of 100 mM NaCl GABA (10^{-5} M) only causes a 1.9-fold reduction in the IC_{50} of FLU at 37°C (Ehlert et al. 1981). In contrast, no significant effects of GABA (10^{-5} M) on the binding of Ro15-1788 were detected in the presence or absence of 100 mM NaCl (*see* Table). Identical results were obtained in the presence of 10^{-4} M GABA (data not shown).

The present results illustrate that under conditions in which GABA causes a moderate increase in the potency of FLU, no significant effects of GABA on the binding of the imidazodiazepine analogue Ro15-1788 are demonstrable. Since the results of pharmacological studies indicate that Ro15-1788 is a specific antagonist of tranquilizing benzodiazepines (Hunkeler et al. 1981), the present data are consistent with our previous suggestion that measurement of the influence of GABA on the binding of ligands to the benzodiazepine receptor may be a useful technique for determining if a drug has pharmacological properties agonistic or antagonistic to benzodiazepines (Ehlert et al. 1981).

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Down Regulation and Heterogeneity of Opiate Receptors

Kwen-Jen Chang, Ph.D.,[1] and Steven G. Blanchard, Ph.D.[1]

One of the adaptative responses of cells or neurons to chronic exposure to ligands is regulation of receptor number. While for most polypeptide hormones and some neurotransmitters the receptor number is decreased after chronic ligand treatment, for the opiate receptor no alteration of receptor numbers after chronic opiate treatment in animals has been observed despite the development of opiate tolerance and dependence. The investigators reexamined this phenomenon in a simple system, the cultured neuroblastoma cell.

Cultured mouse neuroblastoma cells (N4TG1) serve as a useful model for studies on the molecular and cellular action of opiates and opioid peptides (Chang et al. 1978; Chang & Cuatrecasas 1979). Direct receptor binding studies with a labeled enkephalin analog on neuroblastoma cells did not indicate internalization of opiate receptors since nearly all cell associated label was dissociated as intact molecules (Chang et al. 1978). Using the fluorescent enkephalin analog, rhodamine-conjugated [D-Ala^2,Lys^6] leu-enkephalin and image-intensified fluorescence microscopy, enkephalin (δ) receptors in neuroblastoma cells were found to slowly form clusters which do not appear to be internalized (Hazum et al. 1979a,b, 1980). This result differs from many polypeptide (hormones) receptors (*see* review by Hazum et al. 1981) such as for insulin, epidermal growth factor, nerve growth factor, α_2-macroglobulin, chemotactic peptide, and gonadotropin releasing hormone, in which the receptors are internalized following the initial receptor-ligand interactions. This internalization is believed to be related to the so-called down regulation or desensitization.

Chang et al. (1982b) reported that after one to several hours' exposure of neuroblastoma cells in monolayer culture to enkephalin, the number of enkephalin receptors measured subsequently in the extensively washed membrane preparations is greatly reduced. This action is referred to as down regulation. This reduction in receptor number seems selective for opioid peptides and is antagonized by a variety of opiate agonists and antagonists.

Confluent monolayers of cultured mouse neuroblastoma cells (N4TG1) were pretreated with ligand, the cells were then washed extensively with phosphate buffered saline (PBS) to remove ligand remaining bound, and membrane particulate fractions were prepared and washed again with Na+-containing buffer to dissociate any remaining ligand. The enkephalin receptor binding was then measured with ^{125}I-labeled [D-Ala^2, D-leu^5] enkephalin (DADLE) on those cell membrane particulate preparations. Similar results were also obtained when [^{3}H]DADLE or [^{3}H]diprenorphine was used as labeled ligand. Pretreatment of the cell monolayer for 4 hours with 0.1 μM DADLE led to a large reduction of the binding activity of labeled ligands. This reduction induced by the DADLE pretreatment is time, temperature, and dose dependent (Chang et al. 1982b). At 37°C, significant reduction was observed after half-hour pretreatment, and had nearly reached maximum (about 80% reduction) after 1 hour. At 24°C, this reduction in binding is greatly decreased with respect to both the rate and the extent of reduction. The DADLE-induced down regulation is dose dependent with an EC_{50} value of about 2 nM. This value is in reasonable agreement with the previously determined dissociation constant (K_d) of DADLE for enkephalin receptor of this cell line (Chang et al. 1978; Chang & Cuatrecasas 1979).

Down regulation induced by DADLE is specific for opiate receptors, since this effect can be antagonized by the presence of an excess of opiate antagonists such as naloxone, nalorphine, and diprenorphine (Figure 1A). These antagonists do not induce down regulation when they are present alone (Figure 1A). The natural endogenous peptides, met- and leu-enkephalin as well as β-endorphin, and their metabolically stable analogs [D-Ala^2,NMePhe^4,Met(O)ol^5] enkephalin (FK 33824) and [D-Ala^2,Met^5] enkephalinamide can also induce similar down regulation at concentrations of less than μM.

Morphine and benzomorphan drugs such as ketocyclazocine, a κ-agonist, and N-allylnormetazocine, a σ-agonist, at high concentrations induce only a slight and nonsignifi-

[1]Molecular Biology Department, Wellcome Research Laboratories, Research Triangle Park, NC 27709.

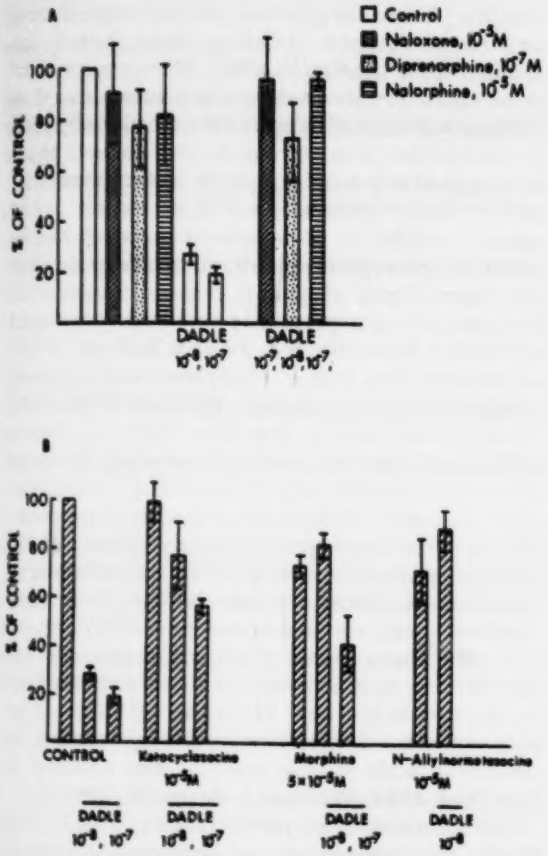

FIGURE 1: Specificity of the ligand-induced opiate receptor down regulation.

N4TGl cells were grown to confluence in DMEM supplemented with 75 units/ml penicillin, 75 μg/ml streptomycin sulfate and either 7 or 5% newborn calf serum (GIBCO) in a 95% air/5% CO_2 humidified atmosphere at 37°. Cells were incubated with or without various opiate agonists (B) and antagonists (A) in the absence and presence of DADLE as indicated in the figure for 4 hours at 37°C. After completion of the incubation the medium was withdrawn, the monolayers rinsed with PBS and the cells were detached using 0.05% EDTA in PBS. The cells were pelleted by centrifugation, resuspended in PBS and incubated for 30 minutes at 37° to remove bound ligand. This incubation was repeated once and then the cell pellet was resuspended in ice cold 50 mM Tris, pH 7.7, and the cells were homogenized using a Model PT-20 Polytron (setting 3.5, 20 sec). The homogenates were centrifuged at 40,000 xg for 30 minutes and the resulting pellets were resuspended in 50 mM Tris, pH 7.7, containing 100 mM NaCl and the suspensions were incubated at room temperature for 1 hour. The membranes were again pelleted, resuspended, and pelleted once in Tris buffer lacking sodium, and assayed for ^{125}I-DADLE binding.

cant receptor reduction (usually about 20%). They can also antagonize the effect of opioid peptides (Figure 1B). This antagonistic effect of opiates against peptides is also dose dependent. Opiates are more effective against a dose of 10^{-8} M than of 10^{-7} M DADLE, as would be expected for competitive inhibition (Figure 1B).

Incubation of cell monolayers with 10^{-8}M [^{3}H]DADLE at 37° for 4 hours followed by washing and preparation of membrane particulates in manner identical to that used for the nonradioactive ligand showed that only 10 percent of the ligand initially associated with the cells remained bound. This corresponds to a concentration of DADLE of less than 10^{-10}M in the final assay. Because incubation of cells with the 10^{-8}M DADLE caused about 70 percent down regulation, the loss of binding activity could not simply be attributed to the competition of ^{125}I-DADLE with ligand that remained after preparation of the membrane fragments. Furthermore, diprenorphine, a ligand known to have an affinity greater than DADLE (Chang et al. 1980), does not cause significant receptor reduction after similar pretreatment, suggesting that peptide-induced receptor loss could not be simply explained by the high affinity of the ligand that may not be washed away.

The enkephalin-induced binding reduction is manifested by a decrease in the number of high affinity binding sites, presumably enkephalin (δ) receptors. The Scatchard plots of the saturation binding curves of ^{125}I-DADLE for control and DADLE (0.1 μM) pretreated cell membranes revealed the loss of total high affinity binding sites without changing the slope (Figure 2). Thus, binding sites remaining after DADLE pretreatment have an affinity similar to that of the control membranes. This is further confirmed by the competition binding studies of DADLE and morphine against ^{125}I-DADLE binding. No significant difference in IC_{50} values (the concentrations which cause 50 percent inhibition of labeled binding) between control and pretreated membranes was observed (Chang et al. 1982a). IC_{50} values of about 50 nM for morphine and 1 nM for DADLE were observed for both control and pretreated membranes in agreement with previously reported values (Chang & Cuatrecasas 1979; Chang et al. 1978, 1979).

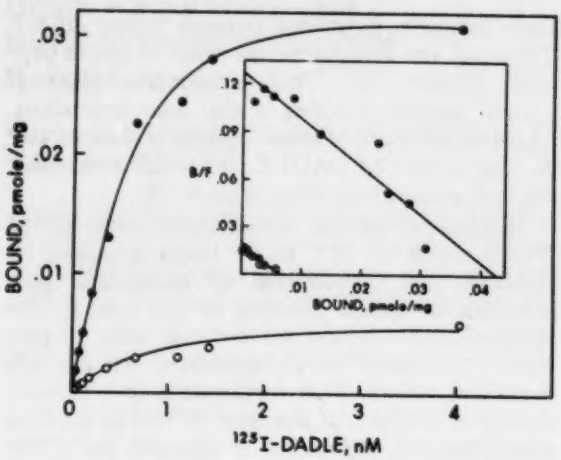

FIGURE 2: Binding of ^{125}I-DADLE to N4TGl membranes before and after preincubation of cells with unlabeled DADLE.

Confluent cultures of N4TGl cells were incubated with or without 10^{-5}M unlabeled DADLE and membranes were prepared as described in the legend to Figure 1. Aliquots of the membranes were incubated for 1 hour with various concentrations of ^{125}I-DADLE after which time bound ligand was determined by rapid filtration through glass fiber filters. Nonspecific binding was determined in the presence of 10^{-5}M unlabeled DADLE. Plots of control (•) and treated (O) membranes are shown. *Inset:* Scatchard plots of the data are shown. The control membranes had a Kd of 0.76 nM and B_{max} of 42.8 fmol/mg while the values for the treated membranes were 0.83 nM and 6.4 fmol/mg, respectively.

The decrease in receptors specifically induced by opioid peptides is intriguing. Numerous *in vivo* and *in vitro* experiments have indicated that enkephalin can mimic the biological effects of morphine, including the development of tolerance and physical dependence (Wei & Loh 1976). To our knowledge, the present results are the first demonstration of opiate receptor down regulation and appear to contradict the conventional concept. Opioid peptides, but not opiate alkaloids, induce down regulation. It will be interesting to know whether this selective effect for opioid peptides is due to the particular opiate receptor subtype in neuroblastoma cells or to neoplastic properties of this cell line. It also will be interesting to know whether the same effect can be observed in the other subtypes of opiate receptors.

Currently it is believed that there are at least five opiate receptor subtypes (Chang & Cuatrecasas 1981). There are $\mu, \kappa, \sigma, \delta$, and ϵ receptors based on pharmacological experiments and four receptor binding sites based on radioreceptor binding studies. The properties of these opiate receptor subtypes are summarized as follows: μ, κ, and σ receptors were originally proposed by Martin to account for the distinct pharmacological actions of morphine, ketocyclazocine, and N-allylnormetazocine. For μ-receptor, morphine is a selective prototype μ-agonist. A highly selective μ-receptor peptide, morphiceptin, has also been identified to be a peptide fragment of β-casein, a major protein in cow milk (Chang et al. 1981a). Kosterlitz, Paterson, & Robson (1981) and others (Handa et al. 1981) have also obtained a highly selective peptide ([D-Ala^2,NMePhe^4, Gly^{5}ol]enkephalin) for μ-receptor. Either μ-Receptors predominate in guinea pig ileum or the intrinsic activity of μ-receptor in guinea pig ileum is greater. Naloxone is a potent antagonist. Mu-receptors are predominately localized in brain areas associated with analgesia and sensory functions (Goodman et al. 1980). They may mediate analgesic and cataleptic activities in animals (Chang et al. 1982a). The possible existence of μ_1 and μ_2-receptors has also been suggested recently by Pasternak (1981). The μ_1-receptor is inhibited irreversibly by naloxazone treatment both *in vivo* and *in vitro* (Zhang & Pasternak 1981; Wolozin & Pasternak 1981).

For κ-receptors, ethylketocyclazocine (EKC) is the typical κ-agonist. Recent data from Wüster et al. (1980) and Chavkin and Goldstein (1981) have suggested that dynorphin may serve as a natural ligand for κ-receptors. Mouse vas deferens and guinea pig ileum tolerant to μ- and δ-agonists do not show tolerance to dynorphin. High cross tolerance occurs between the typical κ-agonists and dynorphin. These receptors show less antagonistic sensitivity to naloxone. They may mediate sedation in animals and hallucinatory and dysphoric effects in man.

Although it was originally postulated that σ-receptor is a subtype of opiate receptor (Gilbert & Martin 1976), the data currently available suggest that it may be a non-opiate type receptor. The typical hyperactivity caused by σ-agonists, is not antagonized by naloxone, only the (+) stereoisomer is active and the effects resemble those of phencyclidine. In studies on stimulus-discriminative procedure, Herling and Wood (1981) showed that rats trained to discriminate phencyclidine generalize to σ-agonists such as

N-allylnormetazocine and cyclazocine. Furthermore, using binding studies, several laboratories (McLowhon et al. 1981; Zukin & Zukin 1981) have also provided evidence that perhaps the σ-agonists bind to the phencyclidine binding sites in addition to their opiate receptor activities.

Delta-receptors were proposed by Lord et al. (1977) to account for the high potency of enkephalin in mouse vas deferens. Many available cultured neuroblastoma cells also contain homogenous δ-receptors (Chang & Cuatresasas 1979). Naloxone is known to be less active in this system than in the μ-receptor system. Delta-receptors are predominately located in the limbic system, as shown by Goodman et al. (1980), and may mediate the action of epileptic seizures (Frenk et al. 1978a, 1978b; Liebeskind 1978) and possibly the reward behavior described by Stein and Belluzzi (1978) and other affective actions of opiates.

Schulz et al. (1979) proposed ε-receptors to account for the unusual selective potency of β-endorphin in rat vas deferens. In this system, both enkephalin and morphine are poor ligands. Interestingly, κ-agonists such as ethylketocyclazocine, bremazocine, and MR2034 behave as rather potent competitive antagonists (Huidoboro et al. 1980; Gillan et al. 1981).

Biochemical receptor binding studies utilizing highly specific radioisotope labeled ligands have confirmed at least three topographically distinct opiate receptor binding sites in brain (Chang et al. 1981b). They are opiate alkaloid morphine preferring binding sites, peptide enkephalin preferring binding sites, and binding sites selective for benzomorphan drugs. Morphine binding sites represent μ-receptors which can be studied with low concentrations of [^{3}H]-labeled dihydromorphine, naloxone, naltrexone or ^{125}I-labeled FK 33-824. Enkephalin binding sites labeled by low concentrations of labeled enkephalins and DADLE are δ-receptors. After quenching μ and δ-receptors with a μ-agonist, morphiceptin and a δ-agonist, DADLE, [^{3}H]diprenorphine binds to a third opiate receptor which we call benzomorphan binding site (Chang 1981). Excluding σ-receptor as an opiate receptor, at present, it is still not clear whether the benzomorphan binding site corresponds to κ or ε receptors, since both have similar high affinity for benzomorphan drugs and low affinity for enkephalin and morphine. Kosterlitz et al. (1981) and Pfeiffer and Herz (1981) have claimed that a similar κ-binding site is identified by using [^{3}H]EKC. However, etorphine which is believed to have no κ-agonist activity has high affinity for this [^{3}H)EKC binding site. Beta-endorphin also shows high affinity compared to enkephalin. It remains to be established whether benzomorphan binding sites are identical to the κ-binding sites.

Using ^{125}I-labeled [D-Ala^2]β*-endorphin, Hazum et al. (1979c) have reported the existence of a non-opiate but β-endorphin specific binding site. A similar non-opiate β-endorphin specific binding has also been observed in a neuroblastoma cell line N18TG2 by Hammonds and Li (1981) who use [^{3}H]labeled β-endorphin.

Previous *in vivo* morphine chronic experiments have led to the conclusion that neither the number nor the affinity of receptors are altered after chronic treatment with morphine (Pert et al. 1973; Klee & Streaty 1974; Hölt et al. 1975; Simon & Hiller 1978). Similar experiments to measure the binding activities of three subtypes of opiate receptors including morphine (μ), enkephalin (δ), and benzomorphan binding sites after chronic morphine treatment *in vivo* have been carried out in this investigator's laboratory. The results confirmed the previous conclusion that neither the number nor the affinity of any opiate receptor subtype are altered after chronic morphine treatment. Thus, the effect of reducing receptor numbers may be selective for opioid peptides and differ from the phenomena of *in vivo* morphine tolerance and dependence.

However, the recent demonstration of the lack of cross-tolerance between a δ-agonist (DADLE) and a μ-agonist (sulfentanyl) in mouse vas deferens after chronic *in vivo* treatment with either ligand (Schulz et al. 1980) suggests that tolerance selective for a receptor subtype may occur in certain systems. N4TG1 cells contain δ-receptors only. The present studies demonstrate that only opioid peptides induce the down regulation of enkephalin receptors. Morphine (a μ-agonist), ketocyclazocine (a κ-agonist), and N-allylnormetazocine (a σ-agonist) are ineffective in inducing this effect. In fact, they antagonize the effects of opioid peptides. These observations resemble the studies on mouse vas deferens (Schulz et al. 1980). Selective desensitization due to the loss of opiate receptors may develop for δ-receptors after chronic opioid peptide treatment for certain systems. The previous failure to detect

the change of opiate receptors after chronic treatment may be because peptides have not been used.

There are many possible mechanisms for the ligand-induced loss of receptors reported here. For instance, desensitized low affinity receptors may be induced by peptides which can no longer be detected by the present binding method. Our preliminary experiments suggest that this is not the case. It may also be possible that the receptors are cryptic after treatment with opioid peptides. The formation of (essentially) irreversible receptor-ligand complexes may also occur during the pretreatment. Understanding of the mechanism of receptor reduction may have important implications for understanding the physiological, pharmacological, and pathological actions of opioids.

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Alpha Adrenergic Receptor Subtypes: Physiological Relationships and Mechanisms

Brian B. Hoffman, M.D.[1]

Alpha adrenergic receptors have been grouped into two major subtypes, termed alpha$_1$ and alpha$_2$ receptors. Radioligand binding techniques have been utilized to measure the number of alpha$_1$ and alpha$_2$ receptors in a variety of tissues. [^{3}H]dihydroergocryptine labels the entire alpha receptor population; the alpha receptor subtypes may be delineated by constructing competition curves with unlabelled selective antagonists and analyzing the data with computer modeling techniques (Hoffman et al. 1979). Alternatively, alpha$_1$ and alpha$_2$ receptors may be directly identified with selective radioligands such as [^{3}H] prazosin and [^{3}H]yohimbine.

Using these methods, human platelets have been found to contain alpha$_2$ receptors (Hoffman et al. 1979). Rabbit uterus contains both alpha$_1$ and alpha$_2$ receptors. Studies in intact strips of rabbit uterus demonstrated that catecholamines induced smooth muscle contraction by activating alpha$_1$ receptors; alpha$_2$ receptors do not seem to play a direct role in this response (Hoffman et al. 1981). Estrogens increase the number of alpha receptors in the uterus; interestingly, this change occurs exclusively in the alpha$_2$ receptor population which is not involved in mediating contraction. Rat liver membranes contain both alpha$_1$ (80%) and alpha$_2$ (20%) receptors (Hoffman et al. 1980b). In isolated hepatocytes, the alpha$_1$ receptors mediate glycogen phosphorylase activation, whereas the physiological significance of the alpha$_2$ receptors in liver is unclear. In experiments designed to study the regulation of alpha receptors, it is important to delineate the subtypes rather than merely the total number of receptors since alpha$_1$ and alpha$_2$ receptors may mediate distinct physiological effects and be separately regulated.

Alpha$_1$ and alpha$_2$ receptors seem to have quite

[1]Division of Clinical Pharmacology (S-155), Department of Medicine, Stanford University Medical Center, Stanford, CA 94305.

distinct mechanisms of action, although the molecular details for neither receptor are well understood. Alpha$_1$ receptors have been associated with changes in intracellular calcium metabolism in a variety of tissues; alpha$_1$ receptors have not been found to regulate intracellular cAMP concentration. Alpha$_2$ receptors have been found to inhibit adenylate cyclase activity in a host of cells. The inhibition of adenylate cyclase is dependent on the presence of GTP. Perhaps related to the different mechanisms of the two receptors is the observation that GTP regulates the affinity of agonists such as epinephrine at alpha$_2$ receptors but not at alpha$_1$ receptors. Indeed, radioligand binding studies have shed some light on the mechanism of alpha$_2$ receptor function. Agonist competition curves with [^{3}H]dihydroergocryptine at the human platelet's alpha$_2$ receptor may be resolved into two affinity components, interconvertable by guanine nucleotides (Hoffman et al. 1980a). These data suggest the possibility of an agonist-promoted association of the alpha$_2$ receptor with an additional membrane component. More direct evidence in favor of this possibility was demonstrated by the increase in sedimentation velocity of solubilized agonist labeled receptor on sucrose density gradients, compared to either unoccupied or antagonist labeled receptor (Michel et al. 1981). A future area of active investigation will involve efforts to further characterize this component which presumably leads to the inhibition of adenylate cyclase.

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Psychobiology of Premenstrual Change

Co-Chair: Jean Endicott, Ph.D.
New York State Psychiatric Institute
New York, N.Y.

and

Uriel Halbreich, M.D.
Department of Psychiatry
Albert Einstein College of Medicine
Bronx, N.Y.

Retrospective Report of Premenstrual Depressive Changes: Factors Affecting Confirmation by Daily Ratings[1]

Jean Endicott, Ph.D.,[2] and Uriel Halbreich, M.D.[3]

Daily ratings made across one or more menstrual cycles at times confirm, and at other times fail to confirm, premenstrual changes reported by women on retrospective questionnaires (Abplanalp et al. 1980; Dalton 1964; Golub 1974; May 1976; McCance et al. 1937; Sampson & Jenner 1977). The authors have begun a series of studies to help determine 1) which types and levels of severity of reported premenstrual changes are most likely to be confirmed by daily ratings; 2) the most efficient ways of obtaining such ratings; and 3) the possible consequences of a failure to confirm reported changes when selecting subjects for biological or treatment studies.

Retrospective Reports of Premenstrual Changes. All subjects described their usual premenstrual changes during the prior three cycles on the Premenstrual Assessment Form (PAF). The PAF, described in detail elsewhere (Halbreich et al. in press), is a 95-item questionnaire designed to describe premenstrual changes with a greater degree of specificity than that of other available procedures (Moos 1968; Steiner et al. 1980). The PAF items are scored to obtain summary measures of 7 Bipolar Continua, 18 Unipolar Dimensional Scales, and 18 Typological Categories. After completion of the PAF, the women made daily ratings for at least one menstrual cycle. A PAF was also completed at the end of the cycle over which daily ratings were made with the focus upon the premenstrual period just experienced.

This preliminary report focuses only upon the typological category of "Depressive Syndrome." The criteria, presented in abbreviated form, are: A. — Depressed or low mood (one of five items rated at least mild), or irritable mood (one of two items rated at least mild); and B. — If depressed mood, at least four of eight items, if irritable or loss of interest or pleasure only, at least five of the eight items. The eight items report change in appetite, sleep, psychomotor function, anergia, loss of interest, low level of social activity, self-deprecation, concentration difficulties, and suicidal ideation.

Daily Ratings. After completing the PAF, the women begin making daily ratings on 21 items of particular interest in ongoing studies by the authors. Each item is rated on a scale of 1 for "not present at all" to 6 for "extreme" manifestation of the mood or behavior in question.

Activity Monitors. Two types of premenstrual depressive syndrome are of particular interest to the authors, that with hypersomnia, lethargy, and decreased activity level, and that with anxiety and increased activity level. Large-scale integrated

[1]Supported in part by New York State Department of Mental Hygiene, Grant #30906-04 and Grant #36186-01 from the National Institute of Mental Health.

[2]Director, Research Assessment and Training Unit, New York State Psychiatric Institute, New York, NY 10032.
[3]Director, Division of Behavioral Endocrinology, Department of Psychiatry, Albert Einstein College of Medicine, Bronx, NY 10461.

(LSI) activity monitors (McPartland et al. 1975) are worn by some subjects when they are making daily ratings in an attempt to obtain objective measures of activity level across the cycle.

Subjects. The subjects were participating in a number of different studies and were recruited in varying ways. Some were co-workers of the senior author, others responded to notices posted about the medical center seeking women for studies across the menstrual cycle, and others contacted the investigators as a result of a newspaper article and a television program reporting on the authors' interest in premenstrual changes. Many of the women in the latter groups were seeking treatment or referral for treatment. At the time of the ACNP meeting, 48 women had completed daily ratings across at least one menstrual cycle, in addition to the initial PAF.

Results

Range of Severity. Women responding to posted notices and co-workers of the senior author tended to report fewer changes and changes of much lower levels of severity than women seeking treatment.

Agreement Between Pre- and Post-PAF. Although the pattern of reported changes was similar for the two PAFs, the severity ratings completed after the cycle of daily ratings tended to be lower. For example, on the PAF Summary Scale for Depressed Mood and Ideation, the mean on the pre-PAF was 26 and that on the post-PAF was 23. The number of subjects whose PAF ratings met criteria for Major Depressive Syndrome pre was 41 and post was 27. The severity levels of the daily ratings also tend to be lower than those noted on the pre-PAF. Some women commented afterward that their premenstrual changes had not been as severe as expected. Both of these findings suggest that women may tend to describe their "worst case" when they report on premenstrual changes in the absence of special attention having been paid to them during the prior month or months.

Likelihood of Confirmation of Depressive Syndrome by Daily Ratings. Confirmation required that the average daily ratings on specified items be at least two points higher during the premenstrual than during the postmenstrual period. Furthermore, ratings during the non-premenstrual days should not be indicative of a tendency to have frequent depressive changes throughout the cycle.

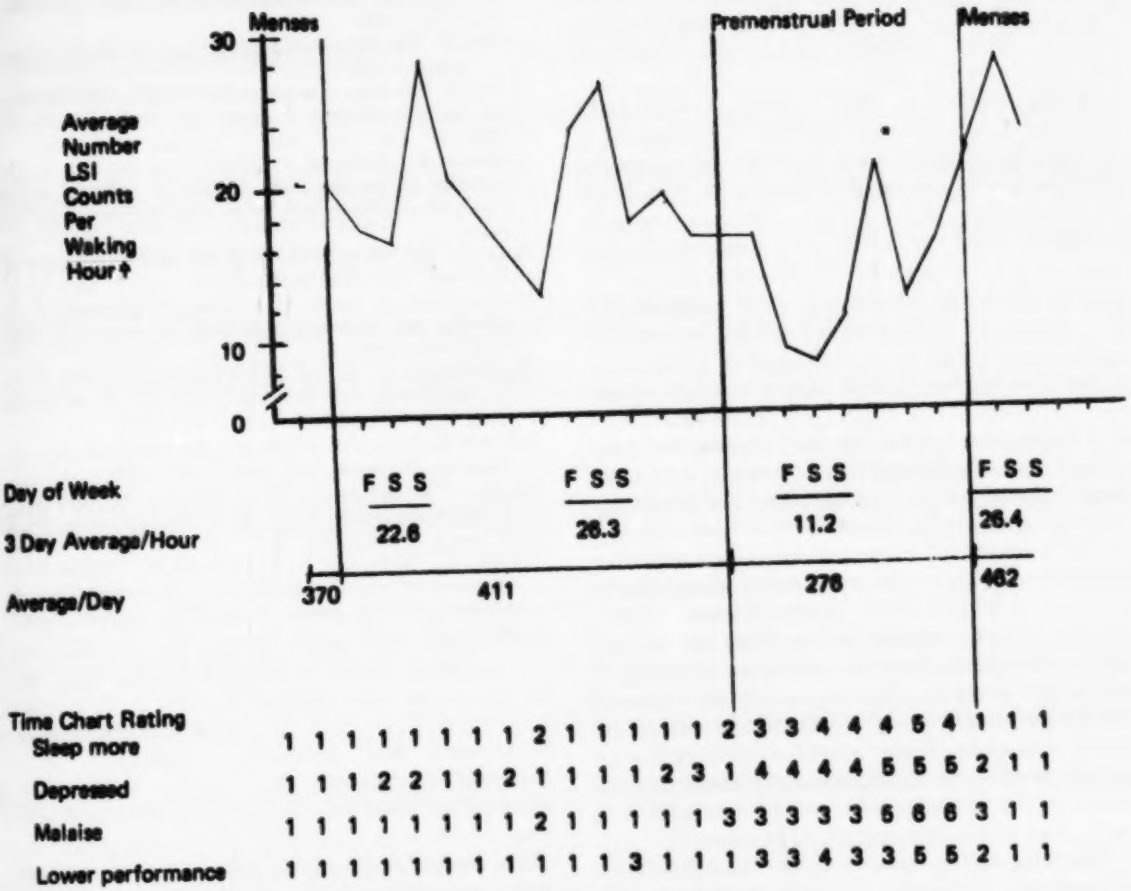
The overall rate of confirmation of the presence or absence of a premenstrual depressive syndrome was only 59 percent for the total sample of 48 women. Fifteen women reported severe depressive changes on the pre-PAF, 13 of these were confirmed, while only 6 of the 14 who reported moderate depressive changes and 5 of the 12 who reported depressive changes at the mild level were confirmed. The pre-PAF ratings for 7 women indicated that they did *not* meet the criteria for a premenstrual depressive syndrome. Their daily ratings confirmed such an absence in only 4, while 3 of the 7 were found to have depressive changes of a syndromal type at the mild level. Two of these women commented on this spontaneously, indicating that they had not noticed premenstrual depression previously. Thus, the likelihood of confirmation of either the presence or absence of a premenstrual depressive syndrome was clearly related to the severity of the reported change, with high levels of confirmation limited to those reporting a severe syndrome.

Although some of the women whose ratings failed to confirm reports of mild or moderate change had daily ratings indicating premenstrual depressive changes on some items, the number of items and level of severity of change were not sufficient to confirm a clear syndromal change of a depressive nature.

The major reason for a lack of confirmation for the women who described severe or extreme changes were ratings indicative of frequent or chronic depressive symptoms throughout the cycle. Although some of these women had premenstrual exacerbations on some items, there was not a clear difference in level of severity for the entire syndrome.

Confirmation of Changes in Activity. Although only a few subjects have worn the LSI, it is already apparent that reported changes of activity may or may not be confirmed. Some women report lethargy, but are actually more active premenstrually. Others report hypersomnia, but are not less active when they are awake. Daily ratings and LSI readings are given for one subject in which both measures confirmed the retrospective reports made on the PAF (*see* Figure).

Example of Confirmation of Reported Premenstrual Changes of Depression, Mood, and Reduced Activity Level


Menses
Premenstrual Period
Menses
30
20
10
0
Average Number LSI Counts Per Waking Hour†
Day of Week
F S S
F S S
F S S
F S S
3 Day Average/Hour
22.6
26.3
11.2
26.4
Average/Day
370
411
276
462
Time Chart Rating
Sleep more 1 1 1 1 1 1 1 1 2 1 1 1 1 1 2 3 3 4 4 4 5 4 1 1 1
Depressed 1 1 1 2 2 1 1 2 1 1 1 1 2 3 1 4 4 4 4 5 5 5 2 1 1
Malaise 1 1 1 1 1 1 1 1 2 1 1 1 1 1 3 3 3 3 3 6 6 6 3 1 1
Lower performance 1 1 1 1 1 1 1 1 1 1 1 3 1 1 1 3 3 4 3 3 5 5 2 1 1

*Day with outside demands for unusual levels of activity for a week day.

†Since the number of waking hours varied from 15 to 19.5 each day, the average waking hour was calculated.

FIGURE

Discussion

The preliminary findings have clear relevance for studies of premenstrual changes, particularly biological and/or treatment studies.

Subjects should not be selected on the basis of retrospective reports alone, whether they are chosen to have particular types of changes or to be free of them. Daily ratings made across one or more cycles are needed to confirm such reports. This is particularly true for changes of a syndromal nature. Reports of changes in activity levels should also be objectively confirmed through the use of activity monitors.

A possible explanation for the high rate of "placebo" response in treatment studies for premenstrual dysphoria is the rather consistent finding that women report less severe changes after at least one cycle of careful attention to their moods and behavior. Had the women involved in

the current studies been on placebo, the scores on the second PAF would have "indicated" that they had a "placebo response." Thus it is not only advisable to use daily ratings to confirm reported changes, but also to establish a new baseline against which placebo or active treatment response may be judged.

Many studies of daily ratings which have reported a lack of confirmation of premenstrual changes have used college students or volunteers who have not been seeking treatment. The levels of severity reported by such women are usually minimal, mild, or moderate. The relationship between level of severity and likelihood of confirmation found in the current study suggests that this may have been a major reason for the low level of confirmation in such studies.

Another reason for lack of confirmation is that many women who reported premenstrual changes of a depressive nature also had depressive symptoms frequently throughout the month so that the premenstrual period was not clearly different.

Some investigators interview women at two points in their cycle to determine if they are clearly more depressed premenstrually than during midcycle. Unfortunately, in the absence of daily ratings, the conclusions drawn from contrasting the two interviews may be misleading if the aim is to select women who are relatively free of depressive symptoms during the nonpremenstrual days of the cycle. Some women appear to have a few days to a week during midcycle when they feel better and are depressed most of the remaining days, with some worsening premenstrually.

The degree to which other nondepressive changes are confirmed by daily ratings is also under study. The findings reported here, as well as those of prior investigators, strongly support the need for the use of daily ratings and other measures of premenstrual change if one is attempting to select homogeneous groups of subjects with contrasting types of changes and levels of severity. Questionnaires such as the PAF are best used for screening of subjects.

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Premenstrual Tension in Biochemical and Psychotropic Drug Assessment

Richard I. Shader, M.D.,[1] and Jerold S. Harmatz

During its earliest years, this unit focused on identifying differential response tendencies among young men taking neuroleptics. Promising typologies were developed to predict, for example, contrasting responses in extroverted athletic men and rather more introspective aesthetes, and in men differing in anxiety traits. These differences seemed to arise from both constitutional and psychological predilections. We were intrigued by the possibility that some of our procedures might be applied to young women, perhaps differentiated in terms of their athletic background. Very soon, however, we were obliged to recognize that for many women, within-month variation in (especially affective) symptomatology was greater than any expectable neuroleptic effect in healthy volunteers. As part of our attempts to identify women with more pronounced tendencies to experience these exaggerated emotional shifts, we found ourselves embarked on a series of studies of the premenstrual tension syndrome.

A 55-symptom checklist was constructed following a review of the literature available at that time (1966). Together with three rating scales of impairment in physical, emotional, and task/social functioning, it was administered to 457 healthy, young women not currently using oral contraceptive medication (Table 1). Rating scale distributions were superimposed and cut-off criteria established for distinguishing between women who experienced minimal and maximal premenstrual tension symptoms across the domain of their somatic and affective lives. These groups are subsequently referred to as the minimal and maximal groups. A residual group was acknowledged as inconsistent with regard to this distress. Indeed, among the maximal group, five prevalent symptoms, viz. anxiety, irritability, depression, fatigue, and abdominal distension were determined regularly to co-occur (Table 2). Such co-occurrence suggested that these symptoms comprise the basis of a premenstrual syndrome (Table 3). A series of multivariate procedures, including obverse factor analysis and discriminant function analysis, were subsequently carried out to identify some five major patterns of premenstrual experience among our volunteers: Group 1 was characterized mostly by depression and irritability; Group 2 by depression and breast enlargement; Group 3 by abdominal pain and autonomic symptoms; and Group 4 by reduced energy, irritability, weight gain, and abdominal distension. Group 5 was nearly symptom-free.

The authors then undertook to relate selected biochemical and treatment parameters to their understanding of premenstrual tension as differently experienced by especially the minimal and maximal groups of women. Inspired by the early work of Loraine and Bell (1963), they examined urinary progesterone and estrogen in 18 healthy, normally ovulating women. Fractionated estrogens (estrone, estriol, estradiol) were determined by the method of Brown (1955). Pregnanetriol was assessed using the procedure of Fotherby and Love (1960). Klopper's Method (1955) was used for pregnanediol. Ten women had self-ratings that met the minimal premenstrual tension criteria and eight were maximal. For the analysis, complete data were available in 13 cases. Their cycles were divided into follicular and luteal phases by subtracting 15 days from the lengths of their cycles. Temperature records confirmed the occurrence of ovulation during the study month.

Table 4 shows lower luteal pregnanediol levels for the maximal cohort. Table 5 illustrates an essentially bimodal distribution of pre-ovulatory estrogen with significant differences between the two cohorts. In Table 6 luteal pregnanediol is shown to differ according to level of pre-ovulatory estrogen. This last observation is consistent with Dalton's demonstrations that natural progesterone is an effective treatment for premenstrual tension syndrome.

Although plasma MAO had earlier been studied for its relationship to premenstrual tension, the authors wanted to understand platelet MAO activity through the cycles of women contrasted for their characteristic premenstrual experience. For 1 month, on alternate days, blood was drawn from 11 high and 10 low premenstrual tension women. Belmaker (1974), who used

[1]Psychopharmacology Research Unit, New England Medical Center Hospital, Boston, MA 02111.

similar biochemical procedures, collected the data shown in Figure 1. Figure 2, however, illustrates that when the data were separated according to premenstrual cohort, the authors found a follicular decrement for our low group and a luteal increment for the high group. On the average, on paper-and-pencil measures, the high premenstrual group evidenced greater dysphoric tendencies during both phases of their cycles.

Table 1

Premenstrual Symptoms
(% of 457 Healthy Women Reporting)

Symptom	Absent	Present	
		Slight	Marked
Anxiety	24.9	43.8	31.3
Lack of concentration	54.5	33.9	11.6
Decreased alertness	64.8	25.8	9.4
Confusion	75.7	15.8	8.5
Nervous	26.0	39.8	34.1
Wanting to cry	32.6	37.0	30.4
Irritability	12.5	39.6	47.9
Depression	17.7	40.5	41.8
Moody	22.5	39.4	38.1
Antagonistic	45.7	34.8	19.5
Easily upset	19.5	41.8	38.7
Fatigue	28.2	37.9	33.9
Listlessness	48.1	35.2	16.6
Lethargy	53.6	31.1	15.3
Malaise	56.7	31.3	12.0
Energetic	65.4	20.6	14.0
Insomnia	82.7	11.6	5.7
Drowsiness	52.5	33.9	13.6
Weakness	56.0	34.6	9.4
Increased libido	39.6	28.9	31.5
Decreased libido	79.6	15.5	4.8
Muscle tightness	52.3	30.0	17.7
Tightness of finger	81.8	13.1	5.0
Dizziness	85.3	12.0	2.6
Weight gain	34.1	45.7	20.1
Swelling feet	80.5	12.9	6.6
Perspiring hands	80.5	13.8	5.7
Leg ache	70.9	16.8	12.3
Pruritus	95.6	3.5	0.9

Symptom	Absent	Present	
		Slight	Marked
Headache	52.5	30.9	16.6
Blurred vision	94.1	5.0	0.9
Eyes sore	88.8	9.2	2.0
Breasts tender	31.3	41.8	26.9
Breasts sore	60.0	23.6	16.4
Breasts painful	79.0	13.6	7.4
Breasts enlarged	49.0	32.8	18.2
Nausea	84.9	12.0	3.1
Vomiting	96.9	2.4	0.7
Increased appetite	62.6	19.0	18.4
Decreased appetite	75.3	18.6	6.1
Craving sweets	67.4	23.0	9.6
Thirst	57.3	26.0	16.6
Constipation	71.3	18.2	10.5
Diarrhea	77.9	16.4	5.7
Abdominal distention	26.0	38.5	35.4
Increased urine premenstrually	59.3	26.5	14.2
Increased urine at menses	61.3	25.4	13.3
Decreased urine premenstrually	90.8	7.4	1.8
Lower abdominal pain	35.7	37.4	26.9
Lower-sided pain	82.7	8.8	8.5
Lower-left-sided pain	85.1	8.1	6.8
Vaginal discharge	42.2	39.2	18.6
Backache	42.2	37.4	20.4
Weakness of legs	73.3	17.9	8.8
Acne	32.6	50.3	17.1

Table 2

Coincidental Occurrence of Five Prevalent Symptoms (% of 457 Healthy Women Reporting)

Combination	Present
Anxiety + depression	0.2
Anxiety + depression + abdominal distension	0.2
Depression + abdominal distension	0.2
Depression + fatigue + abdominal distension	0.4
Anxiety + irritability	0.4
Anxiety	0.4
Fatigue + abdominal distension	0.4
Irritability	0.7
Depression + fatigue	0.7
Anxiety + depression + fatigue	0.7
Anxiety + irritability + fatigue	0.7
Depression	0.9
Anxiety + fatigue + abdominal distension	0.9
Abdominal distension	1.1
Fatigue	1.1
Irritability + fatigue	1.1
Irritability + depression + fatigue	1.3
Irritability + fatigue + abdominal distension	1.5
Anxiety + irritability + abdominal distension	1.8
Anxiety + depression + fatigue + abdominal distension	2.0
Irritability + abdominal distension	2.0
Anxiety + irritability + fatigue + abdominal distension	2.4
Irritability + depression	2.6
Irritability + depression + abdominal distension	3.3
Anxiety + irritability + depression	3.5
Irritability + depression + fatigue + abdominal distension	5.5
Anxiety + irritability + depression + fatigue	8.5
Anxiety + irritability + depression + abdominal distension	8.8
Anxiety + irritability + depression + fatigue + abdominal distension	43.5

Table 3

Occurrence of Five Prevalent Symptoms in Minimally and Maximally Impaired Women (% Reporting)

Symptom	Minimally impaired*			Maximally impaired*		
	Absent	Present		Absent	Present	
		Slight	Marked		Slight	Marked
Anxiety	44.2	40.0	15.8	11.8	43.1	45.1
Irritability	28.4	51.6	20.0	2.9	22.5	74.5
Depression	34.7	47.4	17.9	8.8	24.5	66.7
Fatigue	41.1	36.8	22.1	14.7	35.3	50.0
Abdominal distension	41.1	37.9	21.1	16.7	34.3	49.0

*The two groups differed significantly ($p < .001$) on each symptom

Table 4

Urinary Pregnanediol: Mean Values in μG/24 Hours

Days prior to flow	-10-9	-8-7	-6-5	-4-3	-2-1
Subjects without PMT	2.75 ($N=2$)	2.02 ($N=5$)	3.06 ($N=7$)	3.36 ($N=9$)	1.97 ($N=7$)
Subjects with PMT	0.84 ($N=5$)	1.16 ($N=12$)	1.67 ($N=13$)	1.39 ($N=14$)	1.61 ($N=8$)
p value*	.08	.17	.08	.0078	N.S.

*T-test for independent samples (two-tailed).

Table 5

Preovulatory Urinary Estrogens: Mean Values in μG/24 Hours

Days after flow onset	+6+7	+8+9	+10+11	+12+13
Subjects without PMT	24.75 ($N=8$)	31.50 ($N=8$)	42.38 ($N=8$)	55.25 ($N=8$)
Subjects with PMT	21.50 ($N=8$)	36.63 ($N=8$)	32.77 ($N=9$)	37.22 ($N=9$)
p value*	N.S.	N.S.	N.S.	N.S.

*T-test for independent samples (two-tailed).

Table 6

Urinary Pregnanediol: Mean Values in μG/24 Hours

Days prior to flow	-10-9	-8-7	-6-5	-4-3	-2-1
Subjects with PMT					
Hi-preov-estrogen	1.10 ($N=1$)	2.17 ($N=3$)	2.73 ($N=4$)	1.50 ($N=4$)	2.07 ($N=3$)
Lo-preov-estrogen	0.85 ($N=2$)	0.75 ($N=4$)	0.65 ($N=4$)	0.80 ($N=4$)	0.70 ($N=2$)
p value*	N.S.	.015	.038	.168	N.S.

*T-test for independent samples (two-tailed).

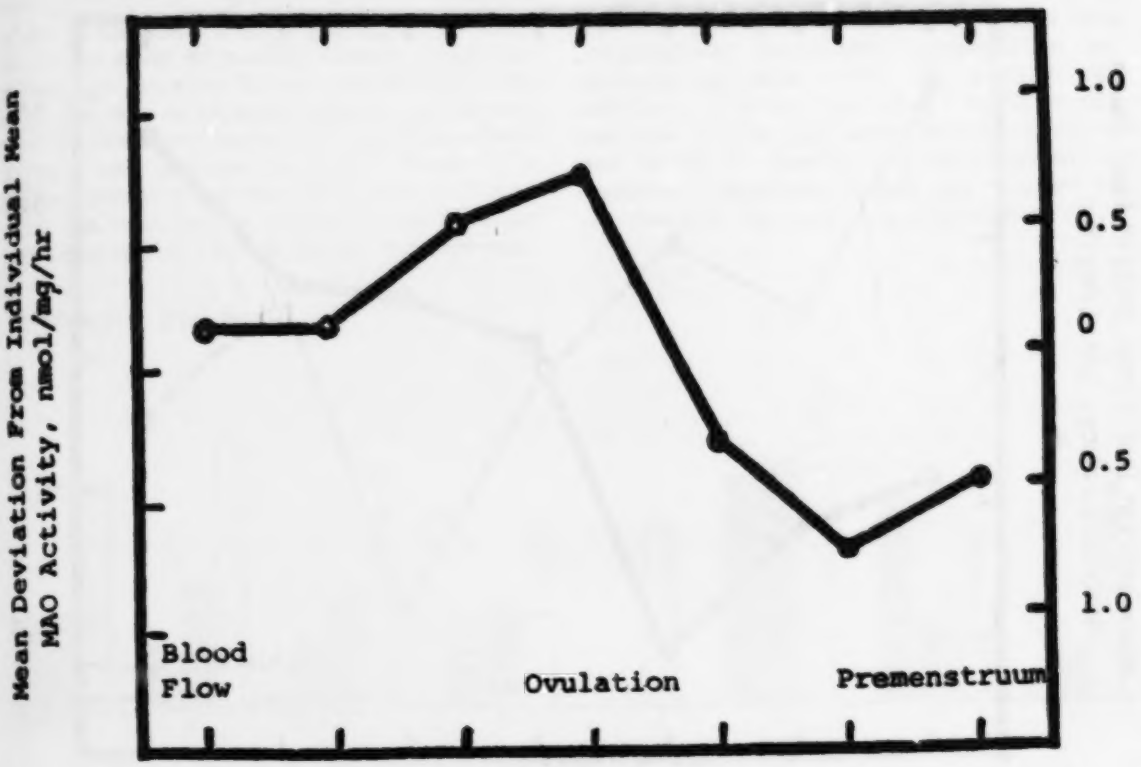
Mean Deviation From Individual Mean
MAO Activity, nmol/mg/hr
1.0
0.5
0
0.5
1.0
Blood
Flow
Ovulation
Premenstruum

FIGURE 1

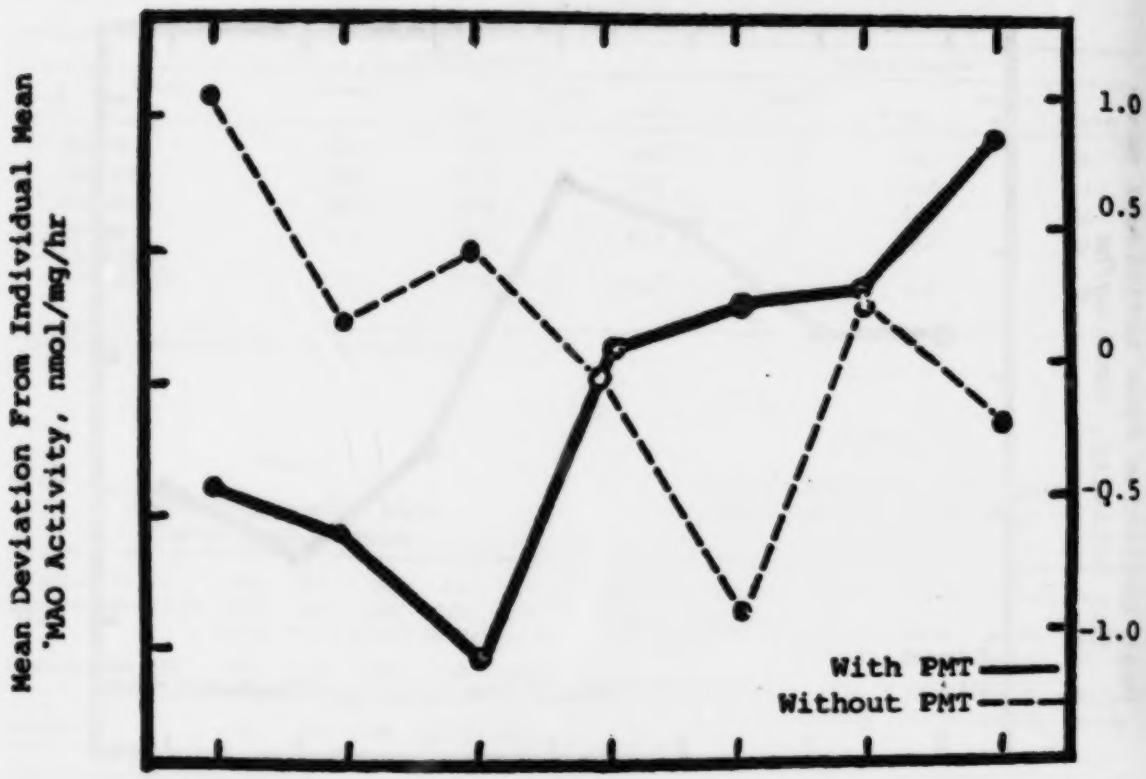
Mean Deviation From Individual Mean
MAO Activity, nmol/mg/hr
1.0
0.5
0
-0.5
-1.0
With PMT
Without PMT

FIGURE 2

With regard to treatment, staff was encouraged by open trials with lithium to undertake a controlled trial of lithium among women who met their premenstrual tension criteria (i.e., members of the MAXIMAL cohort). (*see* Figure 3.) They set out to study 60 healthy women, evenly assigned to receive either lithium carbonate (900 mg/day), placebo, or Dyazide (triamterene 100 mg and hydrochlorothiazide 50 mg/day). Each woman was screened over the course of a preliminary cycle and then, in the next or treated cycle, was evaluated before and after her follicular and luteal weeks. The test battery included standard measures of anxiety, depression, and hostility, as well as self-ratings of functional capacity. Over 60 percent of the screened applicants had to be dropped by the end of the first cycle because of health or procedural anomalies, menstrual cycle irregularities, inconsistent premenstrual experience. In other words, the program was tedious to carry out, and when after 13 women had been run on each active drug condition, as well as 10 on placebo, and no consistent or statistically significant benefit was observed on any measure, the study was terminated.

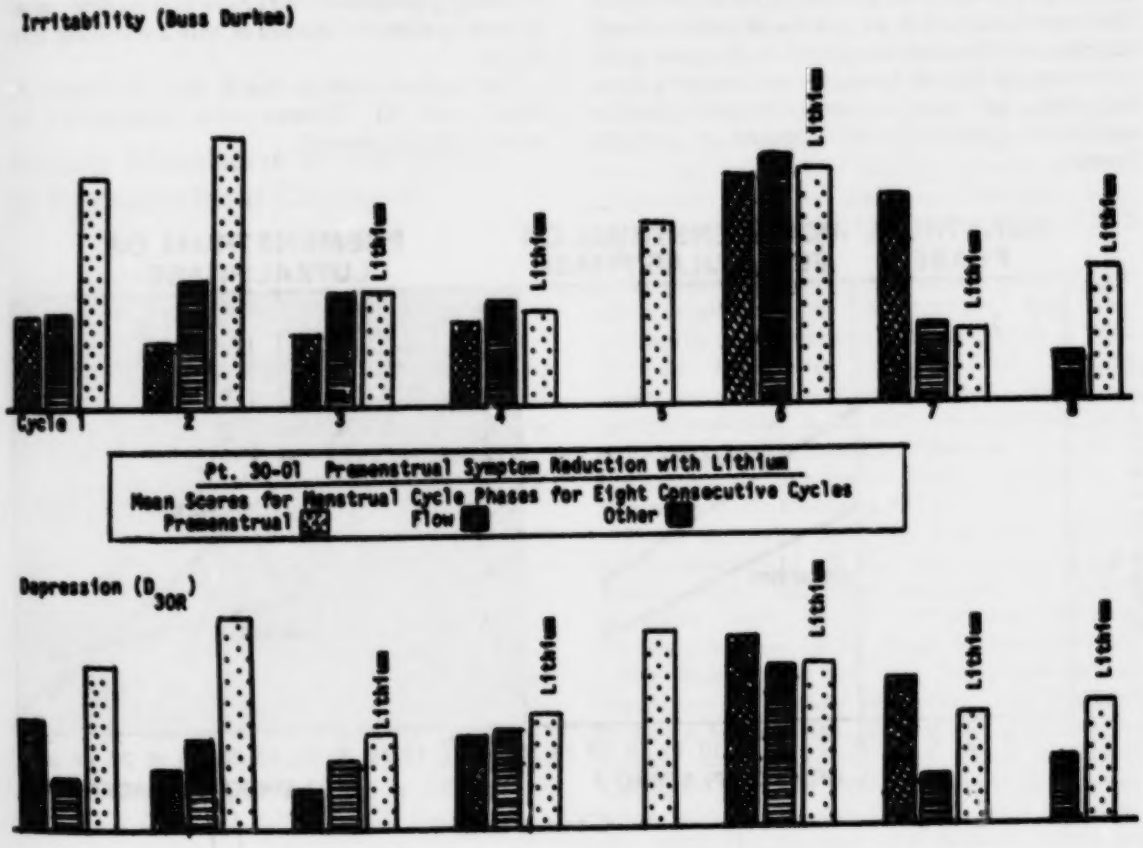

FIGURE 3

In a study of diazepam, 6 mg/day, the authors burdened themselves with an even more cumbersome selection strategy, but with more fortunate results. In this design, they tried to stratify by premenstrual criteria, and by level of anxiety trait to allow comparability with previous work with young men. Considerable overlap obtained between self-reports of premenstrual tension and indices of neuroticism like anxiety. They found it inordinately difficult to find subjects with low anxiety who consistently experienced high premenstrual tension. Forty-nine subjects were stratified by anxiety level and then evaluated on measures of anxiety, depression, and hostility. Only 13 of these cases proved to be invariant in their month-to-month experience of premenstrual distress, and the authors elected to focus on their responses. In Figure 4 may be seen support for a hypothesis of luteal phase diazepam/placebo superiority, especially with regard to anxiety benefit.

The investigations have generally confirmed that menstrual cycle effects might be an important source of variance in psychotropic drug and biochemical trials, especially when female subjects are predisposed to these molimina. It is also true, however, that we have found conventional factorial designs too impractical to fulfill. Their current preference is to include in a multivariate consideration, like a regression equation, a variable which can index a given proband's susceptibility, i.e. which is coded "yes" if the case characteristically suffers from premenstrual tension and whose experimental trial happens to involve her luteal phase. Otherwise, with changes in funding priorities, they have had to defer most of their systematic studies of this interesting syndrome.

The authors wish to thank Drs. D. Osser, P. Soloff, and M. Taymor who collaborated on aspects of this research.

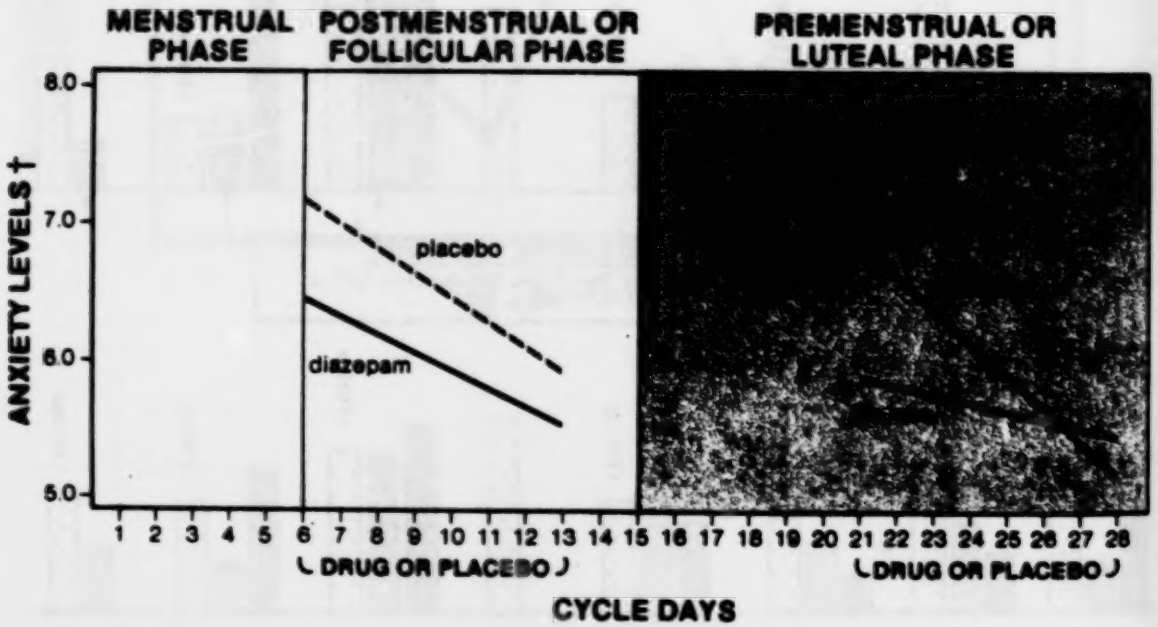
MENSTRUAL PHASE
POSTMENSTRUAL OR FOLLICULAR PHASE
PREMENSTRUAL OR LUTEAL PHASE
ANXIETY LEVELS †
8.0
7.0
6.0
5.0
placebo
diazepam
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28
DRUG OR PLACEBO
DRUG OR PLACEBO
CYCLE DAYS
*Significant reduction of anxiety (P<.001)
†Scores on Sheier-Cattell Anxiety Battery

FIGURE 4

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Future Directions in the Study of Premenstrual Changes[1]

Uriel Halbreich, M.D.,[2] and Jean Endicott, Ph.D.[3]

The physical, behavioral, and mood changes which may occur during the premenstrual period are very prevalent and sometimes may be severe enough to warrant treatment. However, the etiology and pathophysiology of premenstrual changes (PMC) are unclear.

A recent wave of interest in PMC has been manifested by an increase in the number of articles and symposia on the subject. Many of these share a widely held misconception in that the entire gamut of premenstrual changes is treated as a single syndrome. Studies by the authors (Halbreich & Endicott 1982; Halbreich et al., 1982b, 1982c) as well as others (Moos & Leiderman 1978) have indicated that PMC are better conceived as consisting of a number of different but partially overlapping subtypes and dimensions.

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[2]Department of Psychiatry, Albert Einstein College of Medicine, Bronx, NY 10461.

[3]New York State Psychiatric Institute and Department of Psychiatry, College of Physicians and Surgeons, Columbia University, New York, NY 10032.

Subtypes of PMC are differentially related to affective disorder (Endicott et al. 1981), even among women who meet criteria for a premenstrual depressive syndrome. Three subtypes of premenstrual depressive changes have been shown to have different external correlates (Halbreich et al., in press). Furthermore, some of the major types of change are bipolar (e.g., decreased and increased activity or appetite, depression but also elevation of mood).

Once the concept of a single PMC syndrome is replaced by a recognition of diverse PMC whose subtypes should be delineated and well-defined, the door is open to change the assumption that a single variable is responsible for "a premenstrual tension syndrome." It is highly unlikely that such diverse changes with evidence of differential correlates have the same pathophysiology. The diversity of PMC should lead to the assumption of multivariate etiology of these changes. Furthermore, the division of PMC into specific subtypes facilitates study of different, partially overlapping, mechanisms of pathophysiology of each subtype.

An imbalance between some hormones, especially estrogen and progesterone, has been previously suggested as a causative factor of PMC (Review: Rausch & Janowski 1982). Furthermore, there is indirect evidence that a high estrogen/progesterone ratio may be associated with irritability-anxiety-hostility PMC as opposed to predominantly depressive PMC (Bäckström & Mattsson 1975; Cullberg 1972).

From the other side, an imbalance between neurotransmitters (e.g., norepinephrine and acetylcholine) has been suggested in mental disorders with similar syndromes (Review: Pradhan & Bose 1978). Brain monoamines and other transmitters not only participate in the regulation of gonadal hormones, but there are feedback mechanisms, influence on metabolic enzymes, and effects on postsynaptic sensitivity through which the ovarian steroids actively interact with neurotransmitters (Rausch & Janowski 1982). In humans and animals, there are several reports that plasma, urine, and brain levels of neurotransmitters or their metabolites fluctuate along the menstrual cycle (Weiner & Elmadjian 1962; Deleon-Jones et al. 1978; Greengrass & Toung 1971).

It is reasonable to assume, with high likelihood, that changes in ovarian hormones and several

neurotransmitters are involved in an intricate interactive balance whose impairment may be part of the pathophysiology of PMC. Moreover, there has recently been a substantial accumulation of data suggesting that various functions of the central nervous system are modulated by, or at least involve, a growing number of recently discovered substances, various endogenous opioids, prostaglandins, i.e., trace amines. A possible role of some of these substances in PMC has been hypothesized (Halbreich & Endicott 1981; Reid & Yen 1981; Horrobin 1979). These hypotheses were based on the fluctuations of the relevant substances along the menstrual cycle, their possible involvement in phenomenology that resembles PMC, and their interaction with gonadal hormones and neurotransmitters.

One may hypothesize that multiple interactions exist among all the above-mentioned systems (and probably some others) which influence each other. Such an interaction may be in an imbalance during the premenstrual period. The imbalance may be triggered by a succession of events which take place prior to, and during, the premenstrual period. This period may be defined as a period of *change*. Indeed, a premenstrual change in plasma levels or activity may be the only common denominator for the numerous substances whose involvement in the PMC has been hypothesized. In most cases premenstrual changes in levels of hormones and other substances, by themselves are normal, but the magnitude and pace of change vary substantially among women.

One may assume that when levels of several hormones (and other substances) change simultaneously, but at differing pace and magnitude, the homeostasis between hormones, modulators, and neurotransmitters may be temporarily impaired. As a consequence of this impaired homeostasis, vulnerability to external and internal stimuli are increased and greater imbalance may ensue. The imbalanced system is also susceptible to wide fluctuations which may be caused by minor changes in one or several of its components.

Such a model may provide an explanation for the diversity of premenstrual changes. Specific symptoms may be caused by a) changed activity of a single compound in the system; b) a change in an entire system (e.g., renin-angiotensin-aldesterone) which c) may be amplified by a simultaneous change in other compounds or systems (e.g., water retention may be caused by increased activity of the renin-angiotensin-aldesterone axis which may be further aggravated by increased acetylcholine activity which by itself causes increased secretion of antidiuretic hormone). Increase in other variables like prolactin may also contribute to the severity of the same results, namely, water retention; or d) impaired balance between two or more systems (e.g., various monoamines, endorphins, ovarian hormones, etc.) may cause change by itself.

A shift from a conceptual framework of a single causative factor to a multivariate imbalance hypothesis has immediate implications for future studies of PMC. Different strategies of research should be implemented.

The search for different biological mechanisms underlying the various clusters of PMC is self-explanatory. Women with different subtypes of PMC should be compared to each other; comparisons should not be limited to those with no changes at all. Determination of fluctuations in endogenous levels of hypothetical participating variables during the premenstrual period are interesting, but the yield is questionable (especially in plasma) unless the dynamic multiple balance between them is measured. Repeated measurement of dynamic multiple balance and its relationship to mental and behavioral changes in the same women during sequential premenstrual periods and under different environmental conditions may yield valuable information on the interaction among biological changes, vulnerability, and the environment. Dynamic intervention studies (which will not be listed here) may also result in more sophisticated information.

Indeed, a successful approach to the testing of a multivariate imbalance hypothesis of the pathophysiology of PMC necessitates a multidisciplinary team which will completely depart — conceptually and operationally — from the outdated dichotomy between "psychological" and "biological" changes. A multivariate time-sequence statistical analysis should be applied to the data. It is needless to say that an objective, nonbiased (to both sides) investigation should replace the highly prejudiced approach that is still so prevalent in menstrually related research.

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Child Psychopharmacology

Chair: Rachel Gittelman, Ph.D.
New York State Psychiatric Institute
New York, N.Y.

Methylphenidate in Adults with MBD Symptomatology

Jeffrey A. Mattes, M.D.,[1] Lane Boswell, B.A.,[2] and Herman Oliver, M.D.[2]

The fate of children with minimal brain dysfunction (MBD) is uncertain. Until recently, it was believed that children outgrow the symptoms of MBD around the time of puberty (Eisenberg 1966). Recent studies, however, indicate that the outcome of children with MBD is not universally positive. Family (Cantwell 1975) and followup (Weiss et al. 1971) studies suggest that hyperactive children are at risk for behavioral difficulties, including alcoholism and sociopathy, past puberty; though the symptom of hyperactivity may decrease, distractibility, impulsivity, excitability, low self-esteem, poor academic achievement, and interpersonal difficulties may continue into later life. There are also preliminary data suggesting that stimulant medication may be effective in adult conditions possibly related to childhood MBD (Wood et al. 1976; Wender et al. 1981). However, these studies did not include a control group, and so were not able to determine the specificity of drug effect.

The objectives of this study were to evaluate whether methylphenidate (Ritalin), a standard treatment for childhood MBD, is effective in adults with symptoms considered related to MBD, and to evaluate the specificity of drug response. The overall goal was to determine if MBD is a specific diagnostic entity in adulthood with a specific treatment, i.e., stimulant medication.

[1]Psychiatric Ambulatory Care, Bronx Veterans Administration Medical Center, Bronx, NY 10468.
[2]Long Island Jewish-Hillside Medical Center, Glen Oaks, NY 11004.

Method

All patients applying to an adult psychiatric outpatient clinic (approximately 3,000 patients during the course of this study) were screened by questionnaires and interviews to determine eligibility. Two groups of patients were identified: 1) an experimental patient group with adult symptoms of MBD (restlessness, poor concentration, emotional lability, and impulsivity) and retrospective diagnoses of childhood MBD (more specifically, MBD with hyperactive symptomatology), and 2) a control group with similar adult symptoms but with no childhood histories of MBD (this controlled for the possibility that methylphenidate is helpful for certain adult symptoms regardless of childhood history).

It was assumed that the control group would manifest adult MBD-like symptomatology as a result of anxiety or depression; however, severe depressives (major depressive episodes of greater than mild severity), schizophrenics, and manic depressives were excluded. All patients were entered into a double-blind, crossover design, and given 3-week trials of methylphenidate (up to 60 mg/day; the actual mean dosage was 48 mg/day) and placebo.

Baseline evaluation included ratings by patients, psychiatrists, and significant others, on MBD-related and other symptomatology. In addition, old school records were obtained, and parents were asked to retrospectively rate the patient's childhood MBD symptomatology and neuropsychological testing. Evaluation of drug effect included ratings by patients, psychiatrists, and significant others.

Results

Final results, with an N of 63 (approximately 30 in each group) are as follows:

The Diagnostic and Statistical Manual-III (DSM-III) diagnoses of the two groups did not differ significantly except, as expected, that the experimental group much more frequently met the criteria for attention deficit disorder, residual type. The most common diagnoses were major depressive disorder (mild in severity; $N = 19$), alcohol abuse ($N = 17$), drug abuse ($N = 16$), borderline personality disorder ($N = 16$), generalized anxiety disorder ($N = 7$), and antisocial personality disorder ($N = 5$).

A number of baseline measures differentiated the two groups. The experimental group (with childhood hyperactivity) began drinking heavily at an earlier age. Those who did drink heavily had histories of more drug abuse, had missed more time from work, had more conflicts with others, had more childhood antisocial symptoms, and did worse on the Tactual Perception Test. These differences were in the expected direction and indicate that we were successful in identifying relatively distinct groups.

Unfortunately, however, the groups did not differ significantly in response to medication (the principal analyses were four-way analyses of variance: drug x group x order x sex). There was a slight tendency for the experimental group to be judged as having improved more on methylphenidate than the control group, but statistically significant differences were rare.

Attempts to identify predictors of drug response were generally unsuccessful. Correlations between the baseline measures and improvement on methylphenidate were, for the most part, nonsignificant; of the few significant correlations with greater improvement, some were in the expected direction (e.g., more drug abuse and more childhood vandalism), but others were in the opposite-than-expected direction (e.g., fewer temper outbursts and less retrospective parent-rated childhood hyperactivity). Analyses comparing "improvers" on methylphenidate vs. "non-improvers" were also generally unsuccessful in identifying predictors of drug response. In particular, retrospective parent ratings of childhood hyperactivity, reported by Wender et al. (1981) to predict stimulant responsiveness, did not predict response in our sample. Subdividing patients according to the certainty of childhood diagnosis of hyperactivity, or according to the presence or absence of significant depression or anxiety, did not assist in the attempt to identify a homogeneous group of methylphenidate responders. Of the suggestive positive findings, history of drug abuse (polydrug) seemed to be the best predictor of positive methylphenidate response; also, psychiatrist ratings of hyperactive symptomatology tended to predict stimulant response (in the expected direction) more frequently than did ratings by patients, parents, or "significant others."

Despite the generally negative results, we were impressed that a few patients (about 10 in the total sample) did appear to obtain clinically meaningful benefit from the methylphenidate (but not from placebo); these patients had a variety of DSM-III diagnoses. For these patients methylphenidate was recommended clinically following this study, and several of these patients followed this recommendation and continued to benefit from methylphenidate (periodic trials off mediation confirmed this benefit). The response to methylphenidate in some of these cases was as dramatic as in the case histories reported by Wood et al. (1976) and Wender et al. (1981).

Discussion

This study failed to find evidence of methylphenidate response among adults with symptomatology suggestive of MBD. No baseline measure, including history of childhood MBD, predicted methylphenidate response. The clinical evidence of response in certain patients was not evident statistically, and is therefore basically anecdotal. It appears that further work should be done to identify predictors of stimulant response among adults with MBD symptomatology.

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Lithium and Haloperidol in Hospitalized Aggressive Children[1]

Magda Campbell, M.D.,[2] Arthur M. Small, M.D.,[2] Wayne H. Green, M.D.,[2] Susan J. Jennings, M.A.,[2] Richard Perry, M.D.,[2] Walter G. Bennett, M.D.,[2] Maria Padron-Gayol, M.D.,[2] and Lillian Anderson, R.N.[2]

The purpose of this clinical trial was to assess critically the relative efficacy of haloperidol and lithium in children diagnosed as conduct disorder with a behavioral profile of aggressiveness and explosiveness.

Both lithium and haloperidol have antiaggressive properties in adult psychiatric patients with symptoms of aggressiveness and explosiveness (Shopsin et al. 1975; Sheard et al. 1976; Tupin et al. 1973).

There has been little if any systematic investigation of the efficacy of psychoactive drugs involving large samples of aggressive children (for review, *see* Campbell et al. 1978, 1982). This is in spite of the fact that the most frequent reason for admitting children into psychiatric hospitals is repeated occurrences of disruptive and highly explosive behaviors. These children often fail to respond to psychosocial types of interventions and require placement into residential treatment centers.

[1]This study was supported in part by USPHS Grants MH-04665 and MH-32212 from the National Institute of Mental Health.

[2]Department of Psychiatry, New York Medical Center, New York, NY 10016.

Reprint requests to Dr. Magda Campbell, Department of Psychiatry, New York University Medical Center, 550 First Avenue, New York, NY 10016.

Method

Sixty-one (57 males, 4 females) hospitalized children, ages 5.2 to 12.9 years (mean, 8.97) who met the Diagnostic and Statistical Manual (DSM-III, 1980) criteria of conduct disorder, undersocialized, aggressive, completed this double-blind, placebo-controlled study. The following criteria were used for patient selection: 1) a behavioral profile which consisted of severe aggressiveness, explosiveness, and disruptiveness unresponsive to various outpatient treatments including pharmacotherapy and which resulted in the current psychiatric hospitalization; 2) no evidence of psychosis; and 3) no evidence of mental retardation. In addition, the child had to have 1) laboratory values within normal limits; 2) no history of medical illness or no current medical illness contraindicating administration of psychoactive drugs; 3) no seizure disorder or administration of antiepileptic drugs; 4) no need for concurrent administration of any type of drugs; 5) discontinuation of any psychoactive drug for a minimum of 2 weeks prior to the beginning of administration of study medication; 6) meeting the criteria of the Aggression Checklist developed by Hardesty and Shopsin (unpublished); and 7) written informed consent from the child's parents or legal guardians.

On admission to the hospital various examinations, including physical and laboratory tests, were performed on the children. Birth and hospital records were obtained whenever feasible. Family history of psychiatric illness and pre- and perinatal complications were recorded on a scale developed in the authors' unit (Campbell 1977); in addition, the Rochester Research Obstetrical Rating Scale (ROS) (Zax et al. 1977) was completed.

The experiment lasted 6 weeks. All children were placed on placebo for 2 weeks in order to 1) carry out baseline assessments, and 2) eliminate the placebo responders. Children who were suitable for the study were randomly assigned to one of the three treatment conditions: haloperidol, lithium, or placebo. Throughout the study, starting with the first day of the 2-week placebo baseline period, children received three capsules t.i.d. or nine capsules daily. All capsules contained 0.5 mg or 2.0 mg of haloperidol, or 250 mg of lithium carbonate, or placebo. All capsules

were identical in appearance. The medication was administered by the research nurse at 8 a.m., 12 noon, and 4 p.m.

Increments in drug dosages were carried out according to a fixed and coded schedule. Haloperidol dosage began at 1.0 mg/day; increments were gradual over a period of 2 weeks until a maximum of 16.0 mg/day was reached or until the development of untoward effects required reduction or stabilization of dosage. Lithium dosage began at 250 mg/day; increments were made in a similar fashion. The maximum dosage was not to exceed 2,000 mg/day and/or a blood level of 1.8 mEq/l. Dosage was individually regulated over a period of 2 weeks and was followed by a 2-week period on optimal dose. Lithium levels in saliva (Shopsin et al. 1969) were monitored twice a week throughout the study and in blood at termination.

Behavioral symptoms, cognitive functioning, untoward effects and electroencephalograms (EEGs) were assessed on baseline and during treatment at fixed points. Ratings were carried out under several rating conditions by multiple rates using multiple rating scales.

The following measures from the Early Clinical Drug Evaluation Unit (EDCEU) Assessment Battery (*Psychopharmacol. Bull.*, 1973) were used: The Children's Psychiatric Rating Scale (CPRS), Clinical Global Impressions (CGI), Conners Teacher Questionnaire (CTQ), Conners Parent-Teacher Questionnaire (PTQ), Dosage Record and Treatment Emergent Symptoms (DOTES), and the Treatment Emergent Symptom Scale-Write In, using a checklist of untoward effects. In addition, two scales developed by the authors and their staff were employed: a Timed Aggression Behavioral Checklist (ABC), and Global Clinical Judgment.

Results

Several demographic variables were examined to reveal possible influences on drug effectiveness, optimal dose, and outcome. These demographic variables were: socio-economic status (Hollinshead 1965), weight, age, sex, IQs (full scale, verbal, and performance), race, and total score from the ROS. The three treatment groups were compared using chi-square and one-way analyses of variance, which showed no differences between treatment groups at baseline on any of the measures. This precludes the possibility that drug related differences were confounded by these variables among treatment groups.

For children who received haloperidol the optimal doses ranged from 1.0 to 6.0 mg/day (mean, 2.95), or 0.04 mg/kg/day to 0.21 mg/kg/day (mean, 0.096). The maximum dose given during the regulation period ranged from 1.5 to 12.0 mg/day. The optimal doses of lithium ranged from 500 to 2,000 mg/day (mean 1,166). On these doses, lithium level in saliva ranged from 0.81 to 5.05 mEq/l (mean, 2.515); this corresponded to 0.32 to 1.51 mEq/l (mean 0.993) in serum. The maximum doses of lithium given during the regulation period ranged from 750 to 2,000 mg/day (mean 1,452).

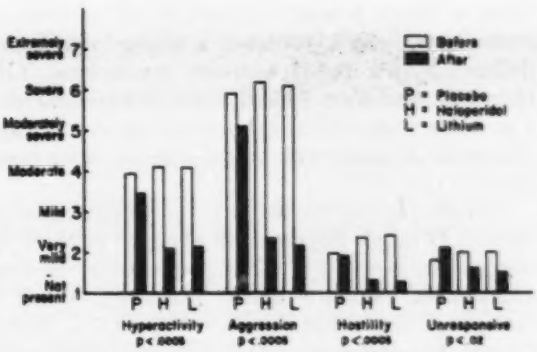

FIGURE 1. Ratings of two child psychiatrists on the Children's Psychiatric Rating Scale, before and after treatment.

Twenty-three CPRS items were entered into an average-linkage clustering analysis which yielded five clusters: Aggression, Hyperactivity, Unresponsive, Hostility, and Speech Problem. In addition, the items tension and bedwetting were also included in subsequent analyses. The details of the cluster analyses will be reported elsewhere. Week 6 ratings for the five clusters and two items were analyzed by an analysis of covariance to determine whether drug significantly affected these areas of behavior. The results are shown in Figure 1. The Hyperactivity cluster (which contained symptoms of hyperactivity, fidgetiness, and distractibility), Aggression cluster (fighting with peers, temper outbursts, and bullying), and Hostility cluster (negative-uncooperative, angry

affect, loud voice, and lability of affect) showed highly significant drug effecs ($p < .0005$); the Unresponsive cluster (underproductive speech, and unspontaneous relation to examiner also showed a significant drug effect ($p < .02$). Speech Problem (level of speech development and mispronunciations), tension, and bedwetting, however, did not show significant drug effects.

Orthogonal contrasts used to compare haloperidol with lithium and to compare haloperidol and lithium with placebo on the four clusters yielded significant differences from baseline to treatment. In each case the two drugs did not differ from each other, but did differ from placebo for the Hyperactivity, Hostility, Aggression ($p < .001$), and Unresponsive clusters ($p < .01$).

The first item of the CGI scale, severity of illness, at Week 6 was analyzed by an analysis of covariance, which revealed a highly significant difference ($p < .0005$) between treatments. Orthogonal contrasts showed that haloperidol did not differ from lithium; however, the two drugs did result in improved ratings and did differ from placebo ($p < .001$).

Children in the two active drug conditions were viewed as much improved in contrast to those in the placebo group ($p < .0005$), based on a one-way analysis of variance which examined Week 6 ratings of the second item of the CGI Scale, Global Improvement. The differences between the two active drug conditions and placebo condition were significant ($p < .001$), but there were no significant differences between the active drugs.

The Efficacy Index is two dimensional, requiring an assessment of both therapeutic effects and side effects. The therapeutic effect differed significantly across conditions ($p < .00005$). Haloperidol did not differ from lithium, but these two differed from placebo ($p < .001$) by orthogonal contrasts. There was also a significant difference among treatment conditions for side effects ($p < .03$) due to the fact that haloperidol has (on optimal dose) more side effects than placebo or lithium which do not differ from each other.

The 39 items of the CTQ were rated by three teachers. Analysis of covariance showed no significant differences among treatment groups for any cluster or individual item. However, only 30 percent of the behaviors improved on placebo while 80 percent improved on haloperidol or lithium.

The PTQ scale was completed by the head nurse of the ward. The Week 6 data were analyzed by an analysis of covariance. Although no significant differences were found, there was a tendency for lithium to be more effective than haloperidol which in turn was more effective than placebo. Behavior actually worsened or remained the same on placebo, but improved in the two drug conditions.

The ABC scale yielded no significant results.

After each child completed the study he was rated on the Global Clinical Judgment Scale as unchanged or worse, minimal, moderate, or marked improvement. This rating was a result of a joint agreement of all staff, while still blind to the child's actual treatment condition. A highly significant difference ($p < .00005$) resulted from a one-way analysis of variance of these scores, as shown in Figure 2, indicating that children treated with haloperidol or lithium improved moderately in contrast to children who received placebo. Orthogonal contrasts confirmed that haloperidol does not differ significantly from lithium, but both lithium and haloperidol differed significantly from placebo ($p < .001$).

Untoward effects were recorded both during dosage regulation and optimal dose (*see* Table). All 20 children who were receiving haloperidol have shown untoward effects at some point: excessive sedation (15; 4 of these on optimal dose), acute dystonic reaction (10; none on optimal), drooling (6; one of these on optimal), and tremor

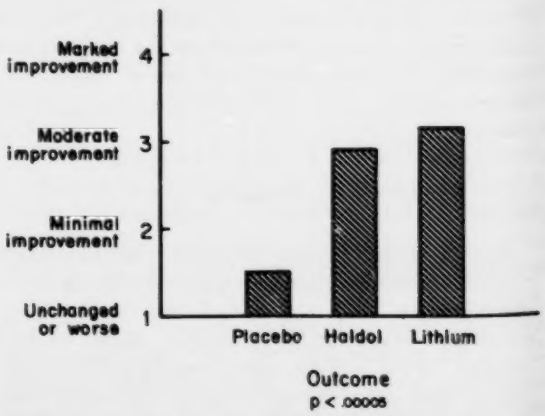

FIGURE 2. Level of overall improvement, as rated by all staff on Global Clinical Judgment Scale.

Table

Incidence of Untoward Effects* by Drug in 61 Patients

Untoward Effects	Haloperidol	Lithium	Placebo	Total
Excessive Sedation	15 (4)	–	4 (3)	19 (7)
Acute Dystonic Reaction	10	–	1 (1)	11 (1)
Tremor	5	5 (3)	1 (1)	11 (4)
Stomachache	–	7 (3)	2	9 (3)
Headache	–	6 (2)	–	6 (2)
Drooling	6 (1)	–	–	6 (1)
Other	18 (4)	25 (5)	6 (4)	49 (13)
TOTAL**	54 (9)	43 (13)	14 (9)	111 (31)
No. of Patients	20	21	20	61
No. of Patients with Untoward Effects	20	17	10	47

*On optimal dose in parenthesis
**Total number of occurrences of different untoward effects

(5; none of these on optimal) were most commonly observed. Of the 21 children assigned to lithium, 17 had untoward effects: pains in the stomach (7; 3 of these on optimal), headache (6; 2 of these on optimal), and tremor (5; 3 of these on optimal dose) were most frequent. In the 20 children who were receiving placebo, 10 patients had some type of untoward effect: excessive sedation (4; 3 of these on optimal dose) and worsening of aggressiveness (4; 3 on optimal) were most common.

During the optimal dose period the average number of untoward effects per child in each of the three treatment conditions did not differ significantly. However, the untoward effects of haloperidol during optimal dose seemed to interfere more with the child's daily functioning than those seen with lithium or placebo. The number of untoward effects on optimal dosage decreased with age on haloperidol ($r = -.40$, $p = .039$), but not lithium.

The cognitive battery and EEG data are currently being analyzed.

In summary, both lithium and haloperidol were superior to placebo in reducing target behaviors in hospitalized aggressive and explosive conduct disorder children on certain measures. The therapeutic effect of these drugs is not only statistically significant but also clinically meaningful.

However, these findings should be replicated. Further research is required to assess the long-term efficacy and safety of these drugs in children.

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Monoamine Receptor Sensitivity and the Mechanism of Action of Antidepressant Treatment

Chair: George R. Heninger, M.D.
Department of Psychiatry
Yale University School of Medicine
New Haven, Connecticutt

The Monoamine Receptor Sensitivity Hypothesis of Antidepressant Drug Action[1]

George R. Heninger, M.D.,[2] and Dennis S. Charney, M.D.[2]

The generalized monoamine receptor sensitivity hypothesis of antidepressant drug action is based on the premise that the therapeutic action of antidepressant treatments (ADT) results from changes in the sensitivity of several monoamine receptors. The overall net effect of these changes is to increase neurotransmission in several monoamine systems. This hypothesis was stimulated by the findings that the electrophysiological sensitivity of single cells to both norepinephrine (NE) and serotonin (5-HT) was increased following long-term antidepressant treatment (Aghajanian 1981), and it is based on the review of a large number of recent studies which have elucidated many of the complex effects of long-term antidepressant treatment (ADT) on monoamine receptor function (Charney et al. 1981a). Similar earlier hypotheses have usually focused on only one monoamine system (Sulser et al. 1978).

The original monoamine deficiency hypothesis of depression (Schildkraut 1965; Bunney & Davis 1965) and its more recent modifications (Maas 1975) were based on the premise that the therapeutic action of drugs is the consequence of an increased availability of synaptic norepinephrine (NE) or serotonin (5- HT) secondary to high affinity reuptake inhibition and/or decreased catabolism. This hypothesis has been questioned on two grounds: a) Some clinically effective antidepressant drugs, such as iprindole and mianserin do not inhibit amine uptake or metabolism (Gluckman & Baum 1969; Goodlet, et al. 1977), and some reuptake inhibitors, such as amphetamine, femoxetine, or cocaine are not effective antidepressant treatments (Overall et al. 1962; Post et al. 1974; Ghose et al. 1977). b) There is an obvious temporal discrepancy between the rapid drug-induced biochemical effects on amine uptake and catabolism, which occur within hours, and the clinical antidepressant response which occurs only after 7-14 days of treatment (Oswald et al. 1972). In addition, studies of NE and 5-HT turnover in animals

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[2]Department of Psychiatry, Yale University School of Medicine, Connecticut Mental Health Center, New Haven, CT 06519.

Address correspondence to: George R. Heninger, M.D., Department of Psychiatry, Yale University School of Medicine, Connecticut Mental Health Center, 34 Park Street, New Haven, CT 06519

following long-term ADT treatment show no consistent changes across the wide spectrum of antidepressant compounds or ECT (Charney et al. 1981a).

Since changes in amine uptake or catabolism do not easily explain the effects of long-term ADT on the behavior of animals or patients, current research has focused on the effects of ADT on monoamine receptor function. Major advances elucidating the complex effects of long-term ADT on NE, dopamine (DA), 5-HT, and histamine (H) receptor function have been facilitated by new developments in radioligand receptor binding, single unit electrophysiological recordings, pharmacologic characterization of cyclic adenosine 3′5′ monophosphate (cAMP) production, and neurotransmitter behavioral paradigms. All of these methods are capable of assessing receptor regulation and function, and they have led to an improved understanding of the effects of long-term ADT.

Receptor Sensitivity in Animals on Long-Term Antidepressant Treatment

Table 1 presents a general summary of the effects of long-term ADT on measures of monoamine receptor sensitivity measured by biochemical, physiologic, and behavioral methods across the receptors for these four monoamine neurotransmitters. (*See* Charney et al. 1981a for a detailed review of this area.) Following long-term ADT there is a decrease in beta receptor binding and a decrease in beta receptor stimulated increase of cAMP. Physiologic studies have, in general, tended to confirm this, but behavioral models for assessing beta receptors are not available.

Long-term ADT produces an increase in alpha-1 receptor sensitivity as indicated by electrophysiologic and behavioral measures. In contrast, no consistent changes in alpha-1 receptor binding have been observed. Alpha-2 sensitivity is decreased or unchanged depending on the drugs studied and the paradigm used. However, changes in alpha-2 sensitivity may reflect an important mechanism of action of some antidepressant drugs, and further studies are necessary to fully evaluate this possibility.

In the dopaminergic system, receptor binding studies demonstrate no change or possibly an increased binding assumed to occur on post synaptic receptors. Electrophysiologic and behavioral studies of the DA system demonstrate presynaptic subsensitivity and a postsynaptic supersensitivity. Thus, chronic ADT treatment appears to augment overall transmission in the dopaminergic system.

Table 1

Effects of Long-Term Antidepressant Treatment on Monoamine Receptor Sensitivity

Monoamine Receptor Type	Measures of Monoamine Receptor Sensitivity		
	Receptor Binding or cAMP Production	Single Unit Electrophysiology	Behavioral
Noradrenergic			
Beta	↓	0↓	—
Alpha 1	0	↑	↑
Alpha 2	↓↑	0↓	0↓
Dopaminergic			
Presynaptic	—	↓	↓
Postsynaptic	0↑	—	↑
Serotonergic	0↓	↑	↑
Histaminergic	0	↑	—

↑ = increase, ↓ = decrease, 0 = no change, — = not tested

Receptor binding in the serotonergic system has generally been found to be decreased, although it was increased following ECT. The increase in serotonergic receptor sensitivity assessed with electrophysiologic measures is consistent with the behavioral studies demonstrating increased sensitivity in this system.

A recent study in the histaminergic system has shown that changes in the sensitivity for cAMP production are not altered by chronic ADT, but that physiologic sensitivity is increased (Olianas et al. 1981). To date, histaminergic behavioral responses have not been studied following chronic ADT.

A careful examination of the studies mentioned above indicates that, particularly in the case of the alpha-1 and serotonin receptor systems, there is either no correlation or an inverse correlation between changes in receptor number determined by ligand binding and functional sensitivity assessed

by electrophysiologic or behavioral techniques. It should be emphasized that changes in receptor number represent only one of several ways that sensitivity to a hormone or neurotransmitter may be regulated. It is possible that the sensitization of NE or 5-HT responses could result from antidepressant-induced changes in the coupling of alpha-adrenergic or 5-HT receptors to effector mechanisms or to changes in the effector mechanism itself. In this regard it is important to note that whereas antidepressant treatment has been shown to increase behavioral alpha-1 adrenergic sensitivity in the spinal cord without any increase in alpha-1 receptor binding, denervation with 6-hydroxydopamine does cause both increased alpha-1 sensitivity and alpha-1 binding (Davis et al. 1981).

A summary of the animal studies indicates that following long-term ADTs there is reduced beta adrenergic sensitivity while overall responsivity to alpha-1 adrenergic, postsynaptic, dopaminergic, serotonergic, and histaminergic stimulation appears to be increased. These changes in sensitivity occur with a time course that is similar to the 7- to 14-day delay in ADT effects observed in patients. Receptor sensitivity changes have usually been shown to occur following long-term administration of all effective antidepressive treatments (i.e., tricyclic antidepressants, 'atypical drugs,' monoamine oxidase inhibitors, and ECT). Thus, the receptor changes are observed irrespective of the markedly divergent pharmacologic profiles of the ADTs that induce them.

Receptor Sensitivity in Patients and Effects of Antidepressant Treatment

In rats, invasive procedures and pharmacologic experiments are conducted to verify that the neurotransmitter agonists and antagonists are indeed affecting the neurotransmitter system under study. Since this is not possible in humans, an alternative strategy has been utilized where a clinically safe neurotransmitter agonist or antagonist is administered. The changes in biochemical and physiological measures produced by the action of the agonist or antagonist on the putative receptor are used as a measure of that receptor's sensitivity. Using this paradigm, human studies have been conducted which support the hypothesis that changes in receptor sensitivity are relevant to the treatment of depressed patients.

A summary of the findings on noradrenergic receptor sensitivity in depressed patients is presented in Table 2. The alpha-2 agonist, clonidine, has been utilized to test the sensitivity of the presynaptic alpha-2 receptor. The dependent measures have been plasma MHPG and blood pressure (BP), both of which are reduced secondary to stimulation of brain alpha-2 adrenergic receptors. As can be seen in Table 2, the effect of clonidine on plasma MHPG and BP is not abnormal in depression (Charney et al. 1982). Treatment with desipramine produced a subsensitivity to clonidine, as measured by both plasma MHPG and BP (Charney et al. 1981b).

Table 2

Noradrenergic Receptor Sensitivity in Depressed Patients

Location	Type	Stimulus	Variable Measured	Level of Sensitivity (Patients vs. Controls)
Presynaptic	α_2	clonidine	plasma MHPG	normal
		clonidine	blood pressure	normal
Postsynaptic	α_2	clonidine	growth hormone	decreased
	α?	amphetamine	corticosteroid	decreased
	α?	dexamethasone	cortisol	decreased
	β	light	melatonin	decreased

Clonidine has been postulated to release growth hormone (GH) via direct action on adrenergic postsynaptic receptors. In depressed patients the GH response to clonidine is decreased (Matussek et al. 1980; Checkley et al. 1981; Charney et al. 1982). At present, it does not appear that this subsensitivity to clonidine is normalized following effective antidepressive treatment (Charney & Heninger 1982). However, there is still the possibility that this test will normalize when patients recover from their illness, i.e., when they can remain symptom-free off medication. Depressed patients have been found to have an impaired release of corticosteroids following stimulation by methylamphetamine. This response was normalized when patients were recovered and retested off medication (Checkley 1979). The resistance of plasma cortisol to dexamethasone suppression occurs in approximately 50 percent of patients and has been found to normalize with effective clinical treatment (Greden et al. 1980). The neurotransmitter receptors involved in the Dexamethasone Suppression Test have not been clearly established, although there is some evidence that an abnormal test could reflect subsensitive alpha adrenergic receptors.

The biochemical and neurophysiologic studies indicate that beta adrenergic receptors are decreased in sensitivity following chronic antidepressant treatment. No animal behavioral model has been found to adequately test the sensitivity of this receptor. It is of some interest that manic depressive patients have an increased sensitivity to light when plasma melatonin has been assayed (Lewy et al. 1981). Melatonin production is inhibited by light and increased by stimulation of beta receptors on the pineal. If the sensitivity of the other synapses in the neural chain between the retina and the superior cervical ganglia is unchanged and if the sensitivity of the beta receptor on the pineal is increased, the effects of light would not reduce melatonin secretion so readily. Thus, this very preliminary data would suggest that in manic depressive patients the sensitivity of the beta adrenergic system on the pineal is decreased. A decrease in beta receptor sensitivity following ADT would obviously not correct an abnormality in depression if beta receptors were already decreased before ADT was started.

Paradigms assessing central 5-HT receptors have not been well developed. The prolactin response following thyrotropin releasing hormone appears to be mediated by a central 5-HT mechanism. This response was potentiated in patients treated with ECT, which is consistent with the animal studies mentioned above (Coppen et al. 1980). Currently, there is considerable research activity in this area and data from additional studies should soon be available (Charney & Heninger 1982).

Discussion

The generalized monoamine receptor sensitivity hypothesis of antidepressant drug action is supported by three lines of evidence:

1. In animals long-term ADT produces changes in receptor sensitivity of at least four monoamine systems, i.e., decreased sensitivity at NE beta and increased sensitivity at NE alpha-1, DA, 5-HT, and H postsynaptic receptors with little evidence of change in acetylcholine, GABA, or glutamate sensitivity.

2. Similar changes in monoamine receptor sensitivity are seen following long-term treatment with very dissimilar drugs, i.e., drugs with very different pharmacologic profiles appear to have a common mechanism of action after long-term administration.

3. The changes in monoamine receptor sensitivity only occur following longer term administration, i.e., 7-14 days, a time course which is consistent with the delayed therapeutic effects of these treatments.

The eventual proof of this hypothesis must await clinical confirmation since the therapeutic mechanisms of action in depressed humans could be quite different than those seen in healthy young rats given larger relative doses of drug treatments. Therefore, it is important that clinical researchers be able to take advantage of the increasing number of methods available for evaluating this hypothesis in patients.

The data from studies of long-term ADTs on receptor sensitivity indicate that the original monoamine deficiency hypothesis requires modification and expansion. The enhancement of sensitivity by ADT of alpha adrenergic and serotonergic postsynaptic receptors is consistent with the original hypothesis that depressed patients have subnormal NE and/or 5-HT func-

tional activity. Thus, the discovery of atypical agents, such as iprindol or mianserin, which were originally thought to weaken this hypothesis, may actually support it if the chronic effects of these agents on monoamine receptor sensitivity are taken into account. As mentioned, the induction of beta-adrenoceptor subsensitivity by ADT has prompted proposals (tantamount to a reversal of the monoamine deficiency hypothesis) that depression is the result of increased noradrenergic activity, at least in the beta noradrenergic system (Sulser et al. 1978). The opposite effects of long-term ADT on alpha and beta receptors do not necessarily have to be interpreted as incompatible. The reciprocal regulation of these adrenergic receptors observed in many studies may be an important mechanism for the homeostatic control of central noradrenergic activity. Thus, the effects induced by chronic antidepressant treatment on the relative sensitivity of alpha and beta adrenoceptors may serve to correct a disorder of adrenergic regulation in affective illness, where the balance between alpha and beta receptor sensitivity is more important than just the absolute effect in either system.

One of the most fundamental and far-reaching implications of the receptor sensitivity hypothesis is the opportunity that it allows for study of the mechanism of action of ADTs at the molecular level. If the induction of increased monoamine receptor sensitivity is an important common mechanism of action of ADTs, then the molecular mechanisms involved in the genesis of this process should allow for the development of much more specific, definitive, and efficacious treatments.

Summary

The generalized monoamine receptor sensitivity hypothesis of antidepressant drug action is based on the evidence that all ADTs produce changes in monoamine receptor sensitivity and that the time course of these changes is similar to the delayed therapeutic actions of these treatments. Long-term ADT has been found to reduce beta-adrenergic sensitivity while enhancing responses to alpha-adrenergic, dopaminergic, serotonergic, and histaminergic stimulation. The initial data from clinical studies suggest that postsynaptic adrenergic alpha receptors may be subsensitive in depression. This would support the hypothesis that depression is a result of decreased monoamine receptor sensitivity and that effective antidepressant treatment may reverse this abnormality.

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Catecholamine-Stimulated Production of Melatonin After Administration of Antidepressants

William E. Heydorn,[1] Stanley Caroff, M.D.,[2] and Alan Frazer, Ph.D.[3]

It is now established that repeated treatment with antidepressant drugs produces effects different from those observed after their acute administration. For example, repeated, but not acute, administration of either the tricyclic antidepressants or the monoamine oxidase inhibitors produces a decrease in the number of β-adrenergic receptors and a reduced ability to generate adenosine 3′, 5′-monophosphate (cyclic AMP) in response to catecholamine (*see* Frazer 1981a,b). What remains unclear is whether such effects have any impact on the overall response of the tissue to catecholamine. To assess this, we examined the effect of repeated administration of antidepressant drugs to rats on catecholamine-elicited production of N-acetyl-5-methoxytryptamine (melatonin) by the pineal gland. The pineal gland contains a high density of β-adrenergic receptors (Greenberg & Weiss 1979) coupled to a catecholamine-sensitive adenylate cyclase receptor that generates cyclic AMP (Weiss & Costa 1968). The β-adrenergic receptors of the pineal gland are activated either pharmacologically by exogenous administration of catecholamine or physiologically by the onset of darkness. Darkness, acting through a multisynaptic pathway, causes the release of norepinephrine from sympathetic nerve terminals innervating the pineal gland (Brownstein & Axelrod 1974). The resultant increase in the glandular content of cyclic AMP (Heydorn et al. 1980) initiates a cascade of processes resulting in the production of melatonin (*see* Klein 1979). Thus, melatonin levels are indicative of the activity of the β-adrenergic receptor/adenylate cyclase/cyclic AMP complex of the pineal gland.

[1]Department of Pharmacology, University of Pennsylvania, Philadelphia, PA 19104.

[2]Department of Psychiatry, University of Pennsylvania and Veterans Administration Hospital, Philadelphia, PA 19104.

[3]Departments of Pharmacology and Psychiatry, University of Pennsylvania and Veterans Adminstration Hospital, Philadelphia, PA 19104.

Male Sprague-Dawley rats, housed on a 12-hour light/dark cycle (lights on at 0700 hr), were used in these experiments. Animals received intraperitoneal injections of the tricyclic antidepressant desmethylimipramine (DMI) (10 mg/kg), or the monoamine oxidase inhibitor nialamide (40 mg/kg), either acutely or twice daily for 7 days. Control animals received 0.9 percent NaCl. Rats treated repeatedly were killed 24 hours after the last injection. It was found that such treatments reduced the number of β-adrenergic receptors of the pineal gland at this time. Rats treated acutely were decapitated 5 hours after drug adminstration.

The first series of experiments examined the effect of repeated antidepressant administration on the melatonin concentration of pineal gland and serum over a 24-hour cycle. Rats were treated as described above and killed at 1000, 1600, 2200, 2400, 0200, 0400, or 0600 hours. Pineal glands and serum were collected and, after extraction with chloroform and washing with petroleum ether, assayed for melatonin by a radioimmunoassay procedure (Pang et al. 1977). The data obtained were analyzed by analysis of variance and Duncan's Multiple Range Test.

The onset of darkness caused a marked elevation of the melatonin concentration in both pineal gland and serum of control rats. Pineal gland melatonin levels rose from approximately 200 picograms/gland during the day to a peak of 4000 picograms/gland at night. Serum melatonin values also rose significantly, from a daytime concentration of 7 picograms/ml to a nighttime level of 45 picograms/ml. Repeated treatment of rats with DMI produced a significant decrease in the nighttime rise of melatonin in both the pineal gland ($p < 0.05$) and in serum ($p < 0.01$). Similar results were obtained when rats were treated repeatedly with nialamide (pineal gland, $p < 0.01$; serum, $p < 0.05$). The extent of the inhibition of the nighttime rise of melatonin produced by repeated administration of these antidepressant drugs was about 25 percent. By contrast, if either DMI or nialamide were administered acutely at 1900 hours and the rats killed at midnight, there was no difference in pineal gland or serum melatonin levels in drug-treated rats as compared to that measured in control animals.

In a second series of experiments, melatonin production in the pineal gland was stimulated pharmacologically by the subcutaneous administration of L-isoproterenol. Rats were treated repeatedly with DMI, nialamide, or 0.9 percent NaCl as described above and then, 21 hours after the last injection, were administered either 0.5 mg/kg or 1 mg/kg L-isoproterenol. Three hours later the rats were killed and the pineal glands removed and assayed for melatonin. In control rats, administration of L-isoproterenol caused a marked elevation of pineal gland melatonin concentrations above baseline, about 15-fold with the lower dose of the catecholamine and about 20-fold with the higher dose. Repeated administration of DMI reduced significantly (by about 50%) the ability of either dose of L-isoproterenol to increase melatonin concentrations in the pineal gland ($p < 0.01$). Similar results were seen upon repeated administration of nialamide to rats. However, if rats were treated acutely with either DMI or nialamide, the stimulatory effect of L-isoproterenol on melatonin levels in the pineal gland was essentially identical to that seen in control animals.

Therefore, in the pineal gland it appears that antidepressant drug-induced subsensitivity of β-adrenergic receptors with concomitant reduced responsiveness of the adenylate cyclase/cyclic AMP system results in a significant decrease in the ability of catecholamines to raise the concentration of melatonin in the gland.

Since this inhibitory effect of melatonin production after repeated antidepressant administration was detected in serum, we wanted to examine whether depressed patients treated with DMI would also show a blunted nighttime rise of melatonin while treated with the tricyclic drug. To date, one patient has been studied. This male unipolar depressed inpatient, aged 34, had a good clinical response to DMI, as shown by Hamilton Depression Scale scores decreasing from 22 prior to treatment to 6 after 4 weeks of treatment. Serum was obtained for melatonin analysis every 1.5 hours between 1730-0600 hours, with lights turned off at 2200 hours. This was done prior to treatment and after 4 weeks of treatment with DMI. Prior to treatment, the patient showed markedly elevated serum concentrations of melatonin during the night (about 115 pg/ml) as compared to those measured in the daytime (about 30 pg/ml). After treatment with DMI, the serum concentration of melatonin rose shortly after the lights were turned off, but then fell during the course of the night. As a consequence, while the patient was treated with DMI the mean nighttime concentra-

tion of melatonin in the serum of this patient (58 ± 11 pg/ml; average of the five values taken between midnight and 6:00 am) was significantly lower than those measured over the corresponding times prior to treatment (114 ± 9 pg/ml; $p<0.005$). Such data are consistent with the belief that antidepressant treatments produce β-adrenergic receptor subsensitivity in patients, although other interpretations of the data are possible also. Further work will be needed to determine whether this approach can provide an index of β-adrenergic subsensitivity in patients. If it can, then the possible clinical importance of the β-receptor subsensitivity produced by antidepressant treatments can be evaluated.

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Agonist-Induced Changes in Behavior as a Measure of Functional Changes in Receptor Sensitivity Following Chronic Antidepressant Treatments[1]

Michael Davis, Ph.D.[2]

Introduction

Therapeutic effects of antidepressant drugs typically do not appear until 2 or more weeks after treatment initiation (Oswald et al. 1972; Klein et al. 1980). Hence, the neuropharmacological actions of antidepressant treatments that accompany chronic as opposed to acute administration should be the ones most relevant to their therapeutic effects. In recognition of this, an increasing number of biochemical and electrophysiological studies are being done to determine changes in neural transmission following chronic antidepressant treatments. However, as elegant as these studies might be, it is important to emphasize that changes in behavior ultimately have to be used to determine functional changes in neural transmission. In general, two broad classes of behavior could be brought to bear on this question. One would include "animal models of depression" in which the behavior of the animal bears some resemblance to human depression. Paradigms such as learned helplessness, the swimming despair test, or social behavior of nonhuman primates following early isolation would be examples. Paradigms such as these have already proved to be important for screening prospective antidepressant drugs and ultimately will be very important for analyzing the etiology of depression. At the present time, however, the complexity of these paradigms makes them difficult to use as behavioral tests to deduce changes in specific transmitter systems following antidepressant treatments.

Behavioral tests of the second class are ones

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[2]Yale University School of Medicine, New Haven, CT 06508.

that have been shown to be modulated by specific central neurotransmitter systems judged by their response to selective pharmacological agonists. These tests are not used as model systems of depression, but as model behavioral systems for deducing functional changes in specific neurotransmitter systems. For example, it is well documented that the drug apomorphine elicits stereotyped behavior via activation of dopamine systems in the brain. Thus, changes in the ability of apomorphine to elicit stereotyped behavior following antidepressant treatments can be used to infer how antidepressants alter functional dopamine transmission.

In the present paper, experiments will be reviewed that use changes in behavioral output induced by selective agonists to assess functional changes in receptor sensitivity following chronic as compared to acute antidepressant treatments. Recent studies in the author's own laboratory will then be reviewed which show that the acoustic startle reflex may be an especially good test system to analyze functional changes in different neurotransmitter systems. Finally, changes in alpha-1 and alpha-2 adrenergic receptor sensitivity following chronic vs. acute treatment with selected tricyclic antidepressant drugs using acoustic startle will be presented.

Table 1

Functional Changes in Dopamine Transmission Based on Behavioral Measures

Treatment	Treatment Test Interval	Probe Drug	Behavior	Treatment Effect	Authors
ECS (× 10)	24 hrs	Methamphetamine	Activity Increase	Enhance	Green et al. 1977
ECS (× 10)	24 hrs	Tranylcypromine L-DOPA	Activity Increase	Enhance	Green et al. 1977
ECS (× 10)	24 hrs	Apomorphine	Turning after Unilateral 6-OHDA	Enhance	Green et al. 1977
ECS (× 5)	24 hrs	Apomorphine	Activity Increase	Enhance—Blocked by Prior NE Depletion	Green & Deakin 1980
ECS (× 8)	24-96 hrs	Apomorphine	Stereotyped Behavior	Enhance	Serra et al. 1981
10 Days of Imipramine or Amitriptyline or Mianserin or ECS (× 8)	48-96 hrs	Low Dose of Apomorphine	Activity Decrease	Blunt—Therefore Net Increase in DA Transmission	Serra et al. 1979
ECS (× 3)	48 hrs	Amphetamine or Apomorphine	Drug Discrimination	Enhance	White & Barrett 1981
Desipramine × 14	24-48 hrs	---	Self-Stimulation	Enhance	Fibiger & Phillips 1981
Amitriptyline Imipramine Desipramine Mianserin Danitracen Iprindole × 14	2 hrs	Apomorphine	Stereotyped Behavior	No Change	Maj et al. 1979b
Amitriptyline Clomipramine Maprotiline Imipramine × 7	½ hr	Apomorphine	Stereotyped Behavior	No Change or Blockade	Delini-Stula & Vassout 1979

Functional Changes in Receptor Sensitivity Following Antidepressant Treatments

Table 1 summarizes studies that have assessed functional changes in dopamine (DA) transmission following chronic antidepressant treatments. In this and all subsequent tables, only studies in which chronic treatments have been used will be included. In general, the effects to be reported only occur after chronic and not acute treatment, although this comparison has not been included in every study.

Table 1 shows that chronic antidepressant treatments tend to enhance DA transmission when behavioral testing occurs at least 24 hours after the final treatment. Repeated applications of electroconvulsive shocks (ECS) enhance the ability of DA agonists such as amphetamine, L-DOPA, or apomorphine to increase locomotor activity (Green et al. 1977; Green & Deakin 1980) or of apomorphine to increase turning in 6-OHDA lesioned rats (Green et al. 1977); or to produce stereotyped behavior (Serra et al. 1981). Repeated ECS or chronic treatment with different antidepressant drugs blunts the ability of low doses of apomorphine to depress locomotor activity, suggesting a net increase in DA transmission (Serra et al. 1979, 1981). Three ECS treatments

Table 2

Functional Changes in Serotonin Transmission Based on Behavioral Measures

Treatment	Treatment Test Interval	Probe Drug	Behavior	Treatment Effect	Authors
ECS (× 10)	24-72 hrs	Tranylcypromine + L-tryptophan	Activity	Enhance	Green et al. 1977 Costain et al. 1979
ECS (× 10)	24 hrs	5-MeODMT	Activity	Enhance	Evans et al. 1976
ECS (× 10)	24 hrs	Tranylcypromine + 5-HTP	Head Twitch	Enhance	Lebrecht & Nowack 1980
ECS (× 10)	24 hrs	Tranylcypromine + L-tryptophan or Quipazine or 5-MeODMT	Activity	Enhance—Blocked by PCPA or Metergoline or NE Depletion but not Haloperidol	Green et al. 1980
Amitriptyline Mianserin Danitracen × 10	48-72 hrs	5-HTP	"Wet Dog Shakes"	Enhance	Moglinicka & Klimek 1979
Amitriptyline Imipramine × 28	48 hrs	5-MeODMT	Head Twitch	Enhance	Friedman & Dallob 1979
Zimelidine × 14	24 hrs	5-MeODMT (low dose)	Head Twitch	Enhance	Fuxe et al. 1981
		5-MeODMT (high dose)		Depress	
Mianserin Imipramine Amitriptyline Desipramine × 8	12 hrs	5-HTP	Sleep Time in Chicks	Enhance	Jones 1980
ECS (× 10)	1 hr	Tranylcypromine + L-tryptophan	Head Twitch	No Change	Lebrecht & Nowack 1980
Amitriptyline Imipramine × 28	1 hr	5-MeODMT	Head Twitch	Block	Friedman & Dallob 1979
Fluoxetine Zimelidine Trazodone Amitriptyline × 14	2 hrs	Tranylcypromine + L-tryptophan	"Serotonin Syndrome"	No Change	Hwang & Van Woert 1980

improve the ability of rats to discriminate amphetamine or apomorphine from saline in a drug discrimination paradigm (White & Barrett 1981). Finally, 2 weeks' administration of desipramine increased rates of intracranial brain stimulation in areas of the midbrain that contain DA cells (Fibiger & Phillips 1981). The results of the last two studies would again point to an enhancement of DA transmission. On the other hand, Table 1 also shows that when testing occurs shortly after the last injection of an antidepressant drug, no increase in apomorphine's effect can be demonstrated (Maj et al. 1979b; Delini-Stula & Vassout 1979).

Table 2 shows that chronic antidepressant treatments also increase functional serotonin (5-HT) transmission, provided that testing occurs at least 12-24 hours after the last treatment. Repeated ECS enhances the ability of various 5-HT agonists to increase locomotor activity (Green et al. 1977, 1980; Costain et al. 1979; Evans et al. 1976) or behaviors associated with heightened 5-HT transmission such as head twitches (Lebrecht & Nowack 1980). Repeated administration of different antidepressant drugs also enhances the ability of 5-HT agonists to increase head twitches (Friedman & Dallob 1971; Fuxe et al. 1981), wet dog shakes (Moglinicka & Klimek 1979) or sleep time in young chicks (Jones 1980), although in some cases this enhancement may only occur with certain doses of 5-HT agonists with reversed effects at other doses (Fuxe et al. 1981). Again, the interval between testing and the last antidepressant treatment is critical, since comparable increases in the effects of 5-HT agonists are not seen at short intervals (Lebrecht & Nowack 1980; Friedman & Dallob 1979; Huang & VanWoert 1980).

Table 3 suggests that chronic antidepressant treatments may increase functional alpha-1 adrenergic transmission. However, the data here are less clear, since the pharmacological mechanisms underlying changes in these behaviors induced by the drugs that were used is

Table 3

Functional Changes in α_1-Adrenergic Transmission Based on Behavioral Studies

Treatment	Treatment Test Interval	Probe Drug	Behavior	Treatment Effect	Authors
Imipramine Amitriptyline Danitracen ×10	24-72 hrs	High-Dose Clonidine	Activity	Increase Activity in TCA-Treated Animals	Maj et al. 1979a
Amitriptyline Imipramine Desipramine Clomipramine Mianserin Danitracen Iprindole ×14	2 hrs	High-Dose Apomorphine	Aggression	Enhance	Maj et al. 1979b
Imipramine Mianserin Iprindole ×10	2 hrs	Very High-Dose Clonidine	Aggression	Enhance	Maj et al. 1980
ECS ×7	24 hrs	Reserpine + Apomorphine + Clonidine+	Activity	Enhance	Modigh 1975
Imipramine Amitryptyline ×21	20 hrs	Yohimbine or Clonidine	Cessation of Swimming in "Despair Test"	Yohimbine Potentiates Effects of TCAs Clonidine Blocks Effects of TCAs	Zebrowska-Lupina 1980

not well documented. Chronic antidepressant drugs or ECS increase the ability of high doses of clonidine to increase locomotor activity alone (Maj et al. 1979a) or in combination with reserpine plus apomorphine (Modigh 1975). Antidepressants also increase apomorphine or clonidine-induced aggression, which can be blocked by the alpha-1 antagonist phenoxybenzamine (Maj et al. 1979b, 1980). Clearly, these data are only suggestive for an enhancement of alpha-1 adrenergic transmission, but they assume greater interest in view of other findings. First, Tables 1 and 2 indicate that the enhancement by ECS of the ability of either DA or 5-HT agonists to increase locomotor activity can be blocked by prior norepinephrine (NE) depletion via administration of 6-OHDA (Green & Deakin 1980). Second, Table 3 shows that the therapeutic effect of chronic imipramine or amitriptyline in the swimming despair test is potentiated by the drug yohimbine and blocked by the drug clonidine (Zebrowska-Lupina 1980). Since these drugs increase and decrease NE transmission, respectively, the data support a role for NE in mediating the effects of these tricyclic antidepressant compounds in this test.

Finally, Table 4 indicates that chronic treatment with desipramine blunts the ability of a low dose of clonidine to decrease locomotor activity when testing occurs 48 hours after the last antidepressant treatment (Spyraki & Fibiger 1980) but not when testing occurs shortly after 7 days of imipramine (VonVoightlander et al. 1980). These data suggest that chronic desipramine may decrease functional sensitivity of alpha-2 receptors, although it is not known if this would occur if other antidepressant treatments were used as well.

Table 4

Functional Changes in α_2-Adrenergic Transmission Based on Behavioral Measures

Treatment	Treatment Test Interval	Probe Drug	Behavior	Treatment Effect	Authors
Desipramine ×15	48 hrs	Low-Dose Clonidine	Activity Decrease	Blunt	Spyraki & Fibiger 1980
Imipramine ×7	3.5 hrs	Clonidine	Activity Decrease	No Change	Von Voightlander et al. 1978

Table 5

Acoustic Startle as a Behavioral Test for Analyzing Functional Changes in Receptor Sensitivity Following Agonist Challenge

Receptor System	Agonist	Route	Dose Range	Effect on Startle
Norepinephrine				
Alpha-1	Phenylephrine	Intrathecal	6-50 μg	Increase
Alpha-2	Clonidine	Intraperitoneal	10-40 μg/kg	Decrease
Serotonin				
Forebrain-Inhibitory	Serotonin	Intraventricular	3-50 μg	Decrease
Spinal-Excitatory	Serotonin	Intrathecal	12-100 μg	Increase
	5-MeODMT	Intraperitoneal	0.5-4 mg/kg	Increase
Dopamine	Apomorphine	Intraperitoneal	0.2-3 mg/kg	Increase

Acoustic Startle as a Behavioral Test for Analyzing Functional Changes in Receptor Sensitivity Following Agonist Challenge

Over the last several years our laboratory has been investigating how various neurotransmitter systems modulate the acoustic startle reflex. Acoustic startle is a brainstem reflex that has a latency of only 8 msec in the rat measured electromyographically. Startle is sensitive to a variety of environmental variables and shows habituation, sensitization, pre-pulse inhibition, and modification by prior classical conditioning (cf., Davis 1980). Recently it has been determined that the neural circuit that mediates startle may consist of the ventral cochlear nucleus, the dorsal and ventral nuclei of the lateral lemniscus, a ventral region of the pontine reticular formation, and lower motor neurons in the spinal cord (Davis et al., in press). The simplicity of the reflex allows one to determine, therefore, where in the central nervous system various neurotransmitters might act in its modulation.

Table 5 summarizes specific data to indicate that startle could be used as a single test system to analyze changes in the sensitivity of NE, 5-HT, and DA systems following antidepressant treatments. Startle is increased via stimulation of alpha-1 receptors in the spinal cord. Thus, direct infusion of NE itself or the alpha-1 agonist phenylephrine into the subarachnoid space (intrathecal administration) increases acoustic startle. This effect is blocked by the alpha-1 antagonist WB-4101, but not by the 5-HT antagonist cyproheptadine or the DA antagonist haloperidol or the beta-adrenergic antagonist propranolol (Astrachan & Davis 1981). Moreover, the phenylephrine effect can be enhanced by prior selective depletion of spinal NE following intrathecal administration of 6-OHDA (Astrachan, Davis, and Gallager, in preparation).

In contrast, acoustic startle is markedly depressed by the alpha-2 adrenergic agonist clonidine (Davis et al. 1977). This effect can be blocked by the alpha-2 antagonists piperoxane or yohimbine (Davis et al. 1977; Davis & Astrachan 1981).

Serotonin has opposite effects on startle depending on whether it acts in the forebrain or spinal cord. Direct infusion of 5-HT itself or 5-HT agonists intraventricularly depresses startle (Davis et al. 1980b; Commissaris & Davis 1982). On the other hand, direct infusion of 5-HT or 5-HT agonists into the spinal subarachnoid space increases acoustic startle (Davis et al. 1980a, b).

Finally, startle is increased by DA, since systemic administration of the DA agonists apomorphine or *d*-amphetamine increases acoustic startle (Davis & Aghajanian 1976; Davis et al. 1977). These effects can be blocked by the DA antagonists haloperidol or pimozide (Davis & Aghajanian 1976; Kehne & Sorenson 1978).

Changes in Functional Alpha-1 and Alpha-2 Adrenergic Receptor Sensitivity Following Tricyclic Antidepressant Drugs

Studies are now underway to use startle as a test system to determine changes in functional receptor sensitivity following antidepressant treatments. Thus far the work has focused on changes in functional NE transmission, since other behavioral data suggest that such effects on NE might interact with changes in 5-HT and DA transmission following chronic antidepressant treatments, as well as being important by themselves.

Changes in Alpha-2 Sensitivity

In the first experiment the effects of three tricyclic antidepressant (TCA) drugs on functional changes in alpha-2 adrenergic transmission were assessed by measuring the degree to which clonidine would depress startle following chronic treatment with antidepressants or saline (Davis & Menkes, in press). Four groups of 20 rats each were used. Animals in each group were injected intraperitoneally (i.p.) once a day for 14 days with saline, desipramine HCl (DMI, 10 mg/kg, USV Pharmaceuticals), amitriptyline (AMI, 10 mg/kg, Merck Sharpe and Dohme), or iprindole (IPR, 5 mg/kg, Wyeth Labs). Al' drug weights are based on the weight of the salt. Twenty-four hours after the last injection five rats in each group were injected with saline and five with clonidine (20 μg/kg). Immediately afterward they were placed into the startle test cages described elsewhere

(Davis et al. 1980b) and presented with a total of 90 noise bursts (110 db) at a 20-second interburst interval, creating a 30-minute test session. Twenty-four hours later the same procedure was repeated except rats previously given saline were now given clonidine (20 μg/kg) and vice versa. The other rats in each of the groups were tested identically with the exception that the dose of clonidine was 40 μg/kg.

To determine if any of the tricyclics might alter the effect of clonidine on startle after acute administration, an additional 4 groups of 10 rats each were given saline, 10 mg/kg DMI, 10 mg/kg AMI, or 5 mg/kg IPR. One hour later, half the rats in each group were injected with saline and half with clonidine (40 μg/kg) and then tested for startle over the next 30 minutes as described earlier. Twenty-four hours later the same tricyclic treatments were repeated, and 1 hour later the rats were given clonidine or saline. In this case, however, rats previously given clonidine were given saline and vice versa.

Figure 1 illustrates that chronic DMI treatment attenuated the depressant effect of either 20 or 40 μg/kg clonidine on acoustic startle. Thus, in the saline-treated rats, clonidine markedly depressed startle within about 10 minutes after injection after either 20 or 40 μg/kg, $t = 7.09$, $p < .001$ and $t = 10.19$, $p < .001$, respectively. Clonidine also depressed startle in the rats treated chronically with DMI, $t = 4.27$, $p < .001$; $t = 6.83$, $p < .001$ for doses of 20 or 40 μg/kg, respectively. However, the magnitude of the depressant effect was less in the DMI-treated rats at both of the test doses of clonidine. For example, from 10 to 20 minutes after injection clonidine depressed startle in rats pretreated with saline by about 55 percent after 20 μg/kg and about 75 percent after 40 μg/kg. In contrast, the same doses of clonidine depressed startle by about 30 and 45 percent in the rats pretreated with DMI, and the difference in the magnitude of depression between saline and DMI pretreated rats was significant at each test dose of clonidine, $t = 2.79$, $p < .01$ for 20 μg/kg; $t = 3.29$, $p < .01$ for 40 μg/kg. The attenuated response to clonidine after DMI occurred in both replications and was significant in each case.

On the other hand, chronic treatment with either AMI or IPR did not alter the depressant effect of clonidine on acoustic startle (Figure 2). After these tricyclics, the percentage changes

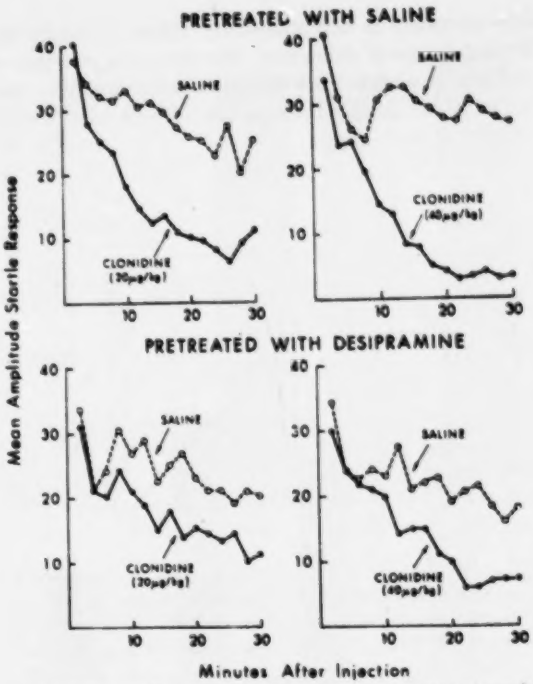

FIGURE 1. Mean amplitude startle response at various times after injection of saline or 20 or 40 μg/kg clonidine in rats pretreated for 14 days with either saline (top) or 10 mg/kg desipramine (bottom).

in startle after either 20 or 40 μg/kg of clonidine were essentially identical to that after saline and significantly greater than the percent changes after DMI ($p < .01$ at each dose when DMI was compared with AMI or DMI was compared with IPR). Finally, none of the tricyclics significantly altered baseline startle levels after chronic administration.

In contrast to chronic DMI treatment, acute treatment with DMI or the other tricyclics did not significantly affect the response to 40 μg/kg clonidine relative to that observed after acute saline (percentage decreases = 80.0, 94.3, 88.9, and 77.4 after IPR, AMI, DMI, or SAL, respectively). Finally, none of the tricyclics significantly altered baseline startle levels at these doses (baseline means = 32.4, 29.8, 30.7, or 32.4 for IPR, AMI, DMI, and SAL, respectively).

These results indicate that chronic but not acute treatment with DMI attenuates the depressant effect of clonidine on acoustic startle. Since

this property is not shared by other clinically effective drugs of this class, the data suggest that a change in alpha-2 adrenergic sensitivity may not be relevant to the therapeutic effects of tricyclic antidepressant drugs.

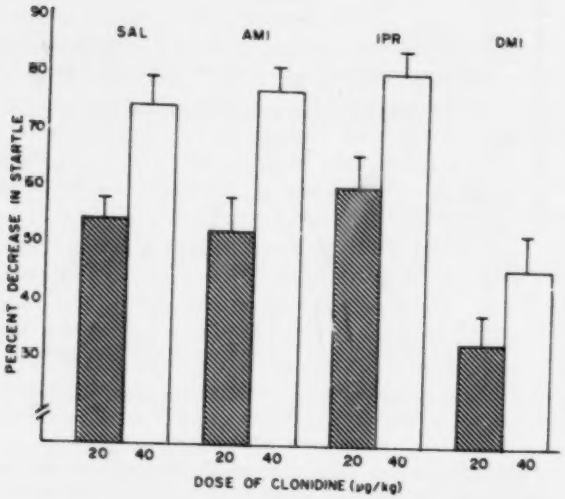

FIGURE 2. Percent decrease in startle after injection of either 20 or 40 µg/kg clonidine in rats pretreated for 14 days with either saline, amitriptyline (10 mg/kg), iprindole (5 mg/kg), or desipramine (10 mg/kg). Baseline means were unchanged by the chronic treatments (29.6, 28.8, 33.0, and 23.9 for the chronic saline, AMI, IPR, and DMI groups, respectively. f = 0.24, N.S.).

The next experiment sought to determine how chronic administration of tricyclic antidepressant drugs would alter alpha-1 adrenergic transmission (Menkes, Kehne, Gallager, Aghajanian, & Davis, in preparation). The same rats used for the study on clonidine were placed back on their respective saline or tricyclic drugs for another 7 days. The rats were then implanted with intrathecal catheters (Davis et al. 1980b) and 1 day later tested for startle by presenting noise bursts once every 20 seconds for 15 minutes. Following this pre-test, the rats were removed from the test cages and infused intrathecally with 25 µg of the alpha-1 adrenergic agonist phenylephrine in a volume of 10 µl at a rate of about 5 µl/minute. The rats were than tested for startle over the next 30 minutes by presenting 90 noise bursts every 20 seconds.

Figure 3 shows the mean amplitude startle prior to and following the infusion of phenylephrine in rats treated chronically for 21 days with either saline or amitriptyline. At this dose, phenylephrine had only a slight excitatory effect in rats chronically treated with saline. However, the magnitude of this effect was considerably larger in rats chronically treated with amitriptyline ($t = 2.35$, $p < .05$). Figure 4 summarizes data obtained after chronic treatment with other drugs. Consistent with the desipramine results, amitriptyline and iprindole also enhanced the effect of phenylephrine. Other experiments showed that this enhanced response to phenylephrine did not occur when testing was carried out 1 hour after a single dose of the tricyclics, a time when brain levels of the tricyclics are known to be higher than 24 hours after a chronic sequence (Vetulani et al. 1976).

Taken together, these data suggest that chronic but not acute treatment with three clinically effective antidepressant drugs increased functional alpha-1 adrenergic transmission. To determine if the enhanced behavioral response to phenylephrine might reflect an increase in the number of alpha-1 adrenergic receptor sites, the

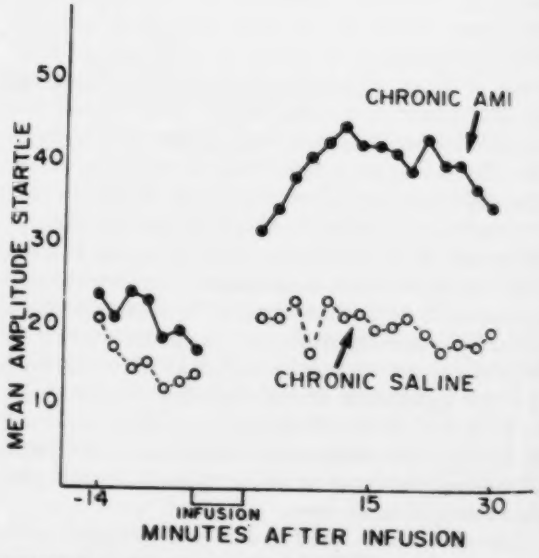

FIGURE 3. Change in startle amplitude before and after intrathecal administration of 25 µg phenylephrine in rats pretreated for 21 days with either saline or amitriptyline.

lumbar portions of the spinal cords from these rats were removed and prepared for 3H-prazosin binding according to the methods of Greengrass and Bremmer (1979). For comparison, rats pretreated 1 week earlier with intrathecal 6-OHDA were also included, since this treatment produces an enhancement of phenylephrine excitation or startle comparable in magnitude to that seen after 3 weeks' treatment of the antidepressant drugs. Figure 5 shows that prior 6-OHDA treatment increased the number of ^{3}H-prazosin binding sites, whereas pretreatment with the antidepressant drugs did not. Other experiments indicated that ^{3}H-prazosin also did not change in rats that were simply pretreated for 21 days with these same tricyclic compounds without getting the clonidine or phenylephrine tests on startle.

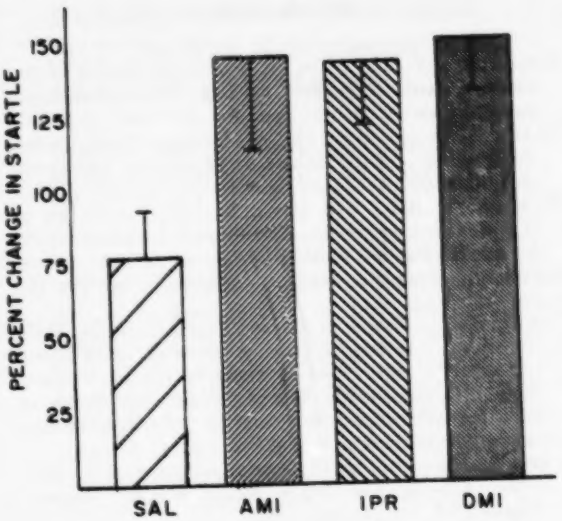

FIGURE 4. Percent change in startle from 0-30 min after intrathecal administration of 25 μg phenylephrine in rats pretreated for 21 days with either saline, amitriptyline (10 mg/kg), iprindole (5 mg/kg), or desipramine (10 mg/kg).

Discussion

To date, the available literature indicates that chronic compared to acute antidepressant treatments produce a pattern of functional changes in receptor sensitivity that includes an enhancement of central DA, 5-HT, and alpha-1 adrenergic sensitivity. These behavioral effects are consistent with enhanced electrophysiological responses to local application of 5-HT, NE, or DA in selected brain regions (cf., Charney et al. 1981). In contrast, changes in functional receptor sensitivity have not correlated with traditional receptor binding techniques, even when these have been done on parts of the nervous system that are known to mediate the behavioral effect (e.g., the present study). Future research should focus on mechanisms that might be common to 5-HT, DA, and NE at a level of neural transmission other than the receptor.

Acknowledgments: The work on chronic antidepressants was done in collaboration with Dr. Dorothy Gallager, John Kehne, and David Menkes. Our sincere thanks are extended to Lee Schlesinger for running the startle tests.

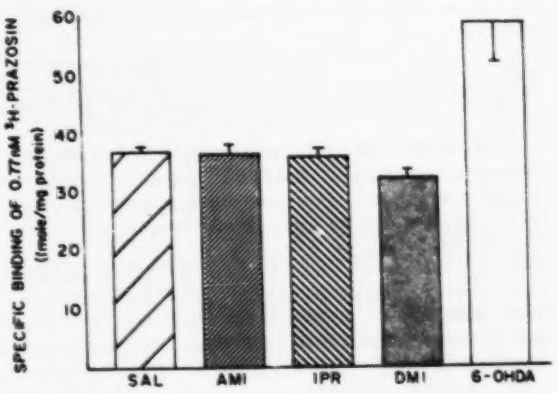

FIGURE 5. Specific binding of ^{3}H-prazosin (0.77 nM) to rat lumbar spinal cord membranes from rats tested for acoustic startle. Animals were killed 3 days after intrathecal injection of phenylephrine and 24 hours after their final chronic antidepressant or saline injection. Non-specific binding was determined by the addition of 1 μM WB-4101. Binding in individual animals was determined by quadruplicate determinations and each value plotted is the mean ± S.E.M. of at least eight treated animals.

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Antidepressant Treatment and Central Adrenergic and Histamine Receptors

Ghanshyam N. Pandey, Ph.D.,[1] P. Sudershan, Ph.D.[1] and John M. Davis, M.D.[1]

The presumed mode of action of antidepressant drugs has been related to their ability to increase postsynaptic concentrations of neurotransmitters such as norepinephrine (NE) or serotonin, either by inhibiting the uptake of such neurotransmitters by inhibiting their metabolism, or by causing increased release. Thus tricyclic antidepressants, like imipramine (IMI) and amitriptyline (AMI) and their metabolites inhibit amine uptake. Monoamine oxidase inhibitors (MAOI), like phenelzine (PHZ) and parnate (PAR), inhibit amine metabolism, and treatment with electroconvulsive therapy (ECT) causes increased release of such amines. The antidepressant drugs thus increase the postsynaptic concentrations of amines and potentiate transmitter function. This presumed mode of action of antidepressant drugs does not explain, however, the delayed onset of clinical effects after the initiation of antidepressant therapy and the antidepressant properties of such drugs as iprindole and Wellbatrin (WB) which do not alter amine uptake or metabolism.

The effect of treatment with antidepressant drugs on beta adrenergic receptor sensitivity has been widely studied, and it has been reported that most antidepressant drugs cause down regulation of the NE-coupled adenylate cyclase system (Vetulani et al. 1976) and beta adrenergic receptor sensitivity (Frazer et al. 1974) after chronic treatment. These effects have been related to the antidepressant properties of these drugs.

In order to further examine the role of beta adrenergic receptors in the mode of action of antidepressant drugs, the authors have studied the effect of treatment with some antidepressant drugs and neuroleptics on ^{3}H-dihydroalprenolol (^{3}H-DHA) binding in rat brain. Since it has been reported that certain antidepressant drugs block histamine receptors, the authors have also studied the effect of antidepressant treatment on

[1] Illinois State Psychiatric Institute and University of Illinois College of Medicine, Chicago, IL 60612.

histamine receptor mediated cyclic AMP accumulation in guinea pig cortex.

Antidepressant Treatment and Beta Adrenergic Receptors

It was first reported by Banerjee et al. (1977) that treatment with antidepressants caused a decrease in beta adrenergic receptor binding sites in rat brain as determined by ^{3}H-DHA binding. The authors in the current investigation examined the effect of chronic treatment with several other antidepressants on beta adrenergic receptor sensitivity in rat cortex by studying the binding of ligand ^{3}H-DHA. The experimental conditions and the results are listed in the Table. It was observed that treatment with desipramine (DMI) caused a significant reduction of the maximum number of ^{3}H-DHA binding sites (receptor density). These results are similar to those reported by Banerjee et al. (1977). Chronic treatment with ECT also caused a significant reduction in the maximum number of ^{3}H-DHA binding sites as previously reported by the authors (Pandey et al. 1979).

The authors examined the specificity of the effects of various antidepressant drugs on ^{3}H-DHA binding to the rat brain by studying the effect of some other classes of antidepressants such as IMI, the MAO inhibitor PHZ, the antidepressant WB, lithium (Li^+), and the neuroleptics, chlorpromazine (CPZ) and haloperidol (HP) (Pandey & Davis 1981). The antidepressant drugs IMI, PHZ, and WB, but not Li^+, caused a significant reduction in the maximum number of ^{3}H-DHA binding sites. Treatment with Li^+ produced a small reduction (14%) in ^{3}H-DHA binding, but this was not significantly different from the binding in control rats ($p < 0.07$, t-test, two-tailed just below level of significance).

To examine whether this reduction in receptor density caused by antidepressant treatment is related to a change in the affinity of ^{3}H-DHA binding, the authors calculated the apparent dissociation constant (K_d) of ^{3}H-DHA binding, as summarized in the Table. There was no significant change in the K_d of ^{3}H-DHA binding in

Table

Effect of Chronic Treatment with Antidepressants on Receptor Density (Maximum ^{3}H-DHA Bound) and Apparent Dissociation (^{3}H-DHA Binding) in Rat Brain

Treatment	Receptor Density ^{3}H-DHA Bound, (fmole mg Protein^{-1})	Percent of Control	p Values as Compared With Control	Dissociation Constant (nM)
Control (1)	119 ± 8.8	100		1.06
Desipramine	84 ± 3.5	71	< 0.001	1.19
Imipramine	66 ± 9.0	56	< 0.001	0.90
ECT	87 ± 3.5	73	< 0.001	1.14
Phenelzine	87 ± 4.6	73	< 0.001	1.19
Control (2)	—	100	—	0.90
Lithium	—	86	< 0.07	0.97
Wellbatrin	—	74	< 0.05	1.06
Cocaine	—	97	NS	
Haloperidol	—	97	NS	
Chlorpromazine	—	88	NS	

Groups of male Sprague-Dawley rats (100-150 g) were given one of the following treatments for 12-14 days: Desipramine (10 mg/kg), imipramine (20 mg/kg), phenelzine (10 mg/kg), WB (60 mg/kg), cocaine (10 mg/kg), haloperidol (5 mg/kg), or chlorpromazine (10 mg/kg) were administered once daily b.i.p. injection and lithium chloride (4 m Eq/kg) twice daily. Control rats received normal saline ECT (75 MA for 1 sec) was administered through transcorneal electrodes once daily for 12 days and controls were treated similarly but did not receive the shock. The rats were killed 1 hr after the last treatment, and the cortices were removed, homogenized in 50 volumes (w/v) of Tris buffer (0.05 M, pH 7.4), and spun at 49,000 g for 10 min. This process was repeated, and the pellet was finally suspended in Tris buffer. Binding of ^{3}H-DHA was carried out in triplicate by incubation of an aliquot of the suspension (0.3-0.5 mg protein) with ^{3}H-DHA at three concentrations (between 0.4 and 4 nM) in Tris buffer in a final volume of 1 ml, with or without 1 μM (−) propranolol, at 23 °C for 15 min. ^{3}H-DHA bound to the membrane was separated by filtration through a Whatman (GF/F) filter and washed three times with 4 ml buffer. The filter was placed in a BBS cocktail and counted in a Nuclear Chicago scintillation spectrometer. Specific binding is defined as the difference between total binding and the binding observed in the presence of 1 μM (−) propranolol. Receptor density and K_d values were calculated by Scatchard analysis; p values were obtained by paired t-test (two-tail). Each group of treatment consisted of 6-8 rats.

animals streated with antidepressants as compared to the control group, indicating that a reduction in the maximum number of ^{3}H-DHA binding sites is not attributable to a change in the affinity of these binding sites.

In order to examine if a decrease in ^{3}H-DHA binding is specific to treatment with antidepressant drugs, the authors examined the effect of treatment with neuroleptic drugs HP and CPZ and the psychomotor stimulant cocaine which, like tricyclic antidepressant drugs, is a potent inhibitor of amine uptake. Neither treatment with HP and CPZ nor with cocaine caused any significant changes in ^{3}H-DHA binding as shown in the Table. These results thus indicated that antidepressant drugs may share a common property of reducing beta adrenergic receptor sensitivity after chronic treatment.

Antidepressant Treatment and Histamine Receptors

Treatment with antidepressant drugs causes alterations in several of the monoamine receptors. It was reported by Green and Mayaani (1977) and Kanof and Greengard (1978) that antidepressant drugs are potent blockers of histamine receptors in the brain under *in vitro* conditions. In order to examine if treatment with antidepressant drugs causes changes in histamine receptor sensitivity, the authors studied the effects of treatment with antidepressant drugs on histamine receptor mediated cyclic AMP accumulation in guinea pig cortex.

Groups of male guinea pigs were injected intraperitoneally (i.p.) with the drugs as indicated (Figure 1) or with normal saline either once daily for 15 days for chronic studies or once for acute studies. The animals were then sacrificed either 1 hour or 24 hours after the last treatment. Histamine-stimulated accumulation of ^{3}H-cyclic AMP in slices of guinea pig cortex that had been prelabelled with ^{3}H-adenine was used as an index of adenylate cyclase-coupled histamine receptor sensitivity by the procedure described by Pandey et al. (1982).

The effects of chronic treatment (15 days) with antidepressant drugs on histamine-stimulated accumulation of ^{3}H-cyclic AMP in the guinea pig cortex obtained when the animals were killed 1 hour after the last injection are shown in Figure 1.

For the purpose of graphical display, histamine stimulated ^{3}H-cyclic AMP accumulation in treated animals has been expressed as percent of ^{3}H-cyclic AMP accumulation of control animals. The differences between control and treated animals were not significant in the basal accumulation of ^{3}H-cyclic AMP (without histamine), although it tended to be lower in treated animals. Histamine (10^{-5}M, 10^{-4})-stimulated accumulation of ^{3}H-cyclic AMP in the cortical slices obtained from guinea pigs that were chronically treated with AMI, DMI, or PHZ was significantly lower than that in the control animals. However, histamine-stimulated accumulation of ^{3}H-cyclic AMP in the slices obtained from guinea pigs treated with CPZ, which has been shown to be a potent blocker of histamine H_2 receptors *in vitro* (Kanof & Greengard 1978), was not significantly different from that in the control animals. Similar results

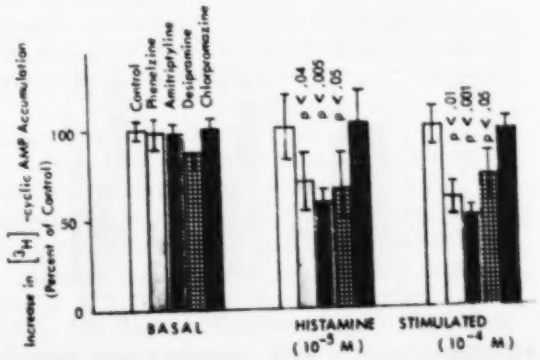

FIGURE 1. Effect of chronic treatment with antidepressants on ^{3}H-cyclic AMP accumulation in cortical slices obtained from guinea pigs sacrificed 1 hour after last injection. Groups of guinea pigs ($N = 7$ in each group) were injected i.p. with amitriptyline (8 mg/kg), phenelsine (15 mg/kg), desipramine (10 mg/kg), chlorpromasine (10 mg/kg), or normal saline (equal volume once daily for 15 days). One hour after the last treatment the animals were killed, and the cerebral cortex was immediately removed from the brain. Accumulation of ^{3}H-cyclic AMP in the absence (basal) or presence of histamine was then determined for each animal. In each set of experiments, treated guinea pigs were paired with control giunea pigs. Since the experiments were conducted in different sets, the results for treated animals have been expressed as percent of ^{3}H-cyclic AMP accumulation relative to controls. The data were analysed by a *t*-test for two independent groups; *p* values (two-tailed) expressed above are those compared to control animals.

were obtained when animals treated for 15 days were sacrificed 24 hours after the last treatment, thus indicating that the effects persist at least up to 24 hours after the termination of the treatment as reported earlier (Pandey et al. 1982).

For acute studies, animals were given single administration of the drugs as indicated and were sacrificed 1 hour after treatment for cyclic AMP accumulation studies. The basal accumulation of ^{3}H-cyclic AMP in the slices obtained from guinea pigs treated acutely with antidepressants was similar to that in control animals, as shown in Figure 2. The accumulation of ^{3}H-cyclic AMP in the presence of histamine (10^{-5}M, 10^{-4}M) was significantly lower in the slices obtained from the animals acutely treated with AMI and DMI, but not in animals treated with PHZ, indicating that the effect of acute treatment with PHZ differs form its effect under chronic conditions.

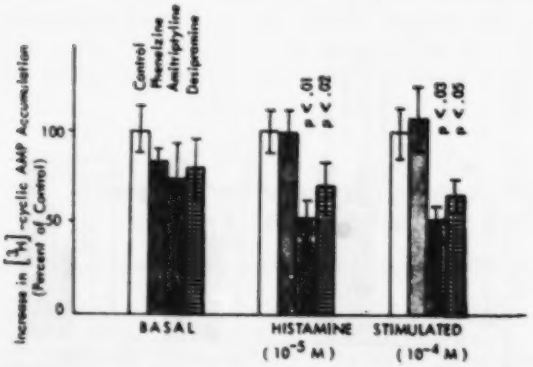

FIGURE 2. Effect of acute treatment (single injection) with antidepressants on ^{3}H-cyclic AMP accumulation in guinea pig cortical slices.

These studies thus indicate that treatment with antidepressant drugs causes a decrease in histamine receptor response in guinea pig cortex. The decrease observed after acute treatment with tricyclic antidepressants may be related to the histamine receptor-blocking properties of these drugs. The effects observed after chronic treatment appears to be related to adaptive changes in the histamine receptor-adenylate cyclase system because PHZ, which is a weak inhibitor of histamine receptors *in vitro*, produces a decrease in histamine-stimulated ^{3}H-cyclic AMP accumulation after chronic but not acute treatment. It therefore appears that at least two different mechanisms may be associated in decreasing histamine sensitive accumulation of ^{3}H-cyclic AMP accumulation in guinea pig cortex.

In summary, the results reported in this paper indicate that chronic treatment with antidepressant drugs causes a decrease in beta adrenergic receptor sensitivity in rat brain and histamine receptor mediated cyclic AMP accumulation in guinea pig cortex. Whereas the role of the histamine receptor in the mode of action of antidepressant drugs remains unclear, the results reported by the authors and other groups of investigators indicate a close relationship between changes in central beta adrenergic receptor sensitivity and antidepressant effects of these drugs. Further work is obviously needed for a better understanding of the molecular mechanisms associated with the mode of action of antidepressant drugs.

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Assessment of Adrenergic and Serotonergic Receptor Function: Implications for the Etiology and Treatment of Depression[1]

Dennis S. Charney, M.D.,[2] and George R. Heninger, M.D.[2]

Recent studies conducted in laboratory animals have provided the basis for several hypotheses relating alterations in adrenergic and serotonergic receptor function to the etiology and treatment of affective illness. Long-term antidepressant (AD) treatment has been shown to decrease the functional sensitivity of alpha-2 and beta adrenergic receptors and to increase the functional sensitivity of alpha-1 adrenergic receptors and serotonergic (5-HT) receptors. (For review, *see* Charney et al. 1981b).

Although it is not possible in human studies to utilize the invasive electrophysiologic and pharmacologic strategies used in animals to develop such hypotheses, several useful methods to assess the clinical relevance of serotonin and noradrenergic receptor function have recently been developed. One method is to design and determine the efficacy of treatment approaches which, based on preclinical investigations, have specific effects on adrenergic and serotonergic receptor function. Another is to use "receptor challenge" paradigms to assess the physiological, biochemical, and behavioral effects of centrally active neurotransmitter receptor agonists and antagonists in healthy controls and depressed patients before and during long-term AD treatment. Recent data obtained from a series of investigations indicate that use of these strategies allows testing of specific receptor hypotheses developed from laboratory animal studies and facilitates the development of improved treatments for patients refractory to standard treatments.

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[2]Department of Psychiatry, Yale University School of Medicine, Connecticut Mental Health Center, New Haven, CT 06508.

Address correspondence to: Dr. Dennis S. Charney, M.D., Department of Psychiatry, Yale University School of Medicine, Connecticut Mental Health Center, 34 Park Street, New Haven, CT 06508.

Receptor Challenge Paradigms

Presynaptic Alpha-2 Adrenergic Receptors

This receptor is located both presynaptically and postsynaptically. There is considerable evidence that the presynaptic alpha-2 adrenergic receptor plays a major role in the modulation of central noradrenergic activity by regulating the release of norepinephrine (NE) through a negative feedback mechanism (Cedarbaum & Aghajanian 1977; Langer et al. 1980; Nyback et al. 1975). Activation of this receptor by alpha-2 adrenergic receptor agonists, such as clonidine, decreases NE impulse flow and turnover (Anden et al. 1976; Cedarbaum & Aghajanian 1977; Svensson & Usdin 1978). Conversely, the alpha-2 adrenergic antagonists, yohimbine and piperoxane, increase NE impulse flow and turnover (Cedarbaum & Aghajanian 1976; Scatton et al. 1980). Consequently, measurement of the effect of alpha-2 adrenergic receptor agonists and antagonists on NE turnover may provide an index of presynaptic alpha-2 adrenergic receptor sensitivity.

The effects of clonidine on behavior, blood pressure, and plasma free 3-methoxy-4-hydroxyphenylethylene glycol (MHPG) in healthy subjects have recently been determined in two separate investigations. Plasma-free MHPG was used as an index of central NE turnover because it has been shown to reflect brain MHPG, the major metabolite of brain NE (Maas et al. 1979; Elsworth et al. 1982). In the first study of 11 male subjects (mean age 28 yrs., range 21-34), oral clonidine (5 μg/kg) produced a 22 percent decrease in plasma-free MHPG 3½, 4, and 5 hours after the dose in comparison to placebo ($p < .01$) (Leckman et al. 1980, unpublished data). In a second sample of 6 male and 6 female subjects (mean age 40 yrs., range 27-57), clonidine (5 μg/kg) produced a 19 percent decrease in mean plasma-free MHPG 3-½, 4, and 5 hours following the dose in comparison to placebo ($p < .05$) (Charney et al. 1982b). In both studies, clonidine also significantly decreased blood pressure and produced behavioral sedation. Thus, the results of the second healthy subject investigation replicated the findings of the original study and supported the reliability of this test as a possible measure of the presynaptic alpha-2

adrenergic receptor system.

A study assessing the effects of oral yohimbine on plasma-free MHPG, cardiovascular function, and behavior in eight healthy subjects has recently been completed. Administration of three doses of oral yohimbine (10, 15, and 20 mg) produced significant increases in mean plasma-free MHPG levels of 33, 33, and 66 percent, respectively, 3 and 4 hours after the dose compared to placebo (Charney et al. 1982a). The 15 and 20 mg yohimbine doses induced significant but clinically safe increases in systolic blood pressure and autonomic symptoms such as piloerection and rhinorrhea. The 20 mg yohimbine dose produced a modest but significant increase in self-rated anxiety. Taken together, the results of these studies indicated that determination of the effects of clonidine and yohimbine on plasma-free MHPG may be a useful method to examine the functional sensitivity of presynaptic alpha-2 adrenergic receptors in depressed patients.

The ability of antidepressant drugs, such as desipramine (DMI), to induce a subsensitivity of the alpha-2 adrenergic receptor may have important implications regarding the mechanism of action of antidepressant drugs and the catecholamine hypothesis of depression (Charney et al. 1981b). To determine whether desipramine induces a subsensitivity in alpha-2 adrenergic receptor sensitivity in depressed patients, the effect of clonidine and clonidine placebo on plasma MHPG in 10 depressed patients was evaluated before and during long-term DMI treatment (Charney et al. 1981a). Long-term DMI treatment significantly attenuated the effects of clonidine on plasma-free MHPG. Prior to DMI treatment, clonidine decreased plasma-free MHPG by 25 percent compared to placebo ($p < .05$). During desipramine treatment, the clonidine-induced decrease in MHPG was only 11 percent and was significantly less than the comparable decrease in MHPG levels observed prior to treatment ($p < .05$). DMI treatment also produced a 36 percent decrease in baseline plasma-free MHPG compared to pretreatment levels ($p < .01$). In the 10 patients studied, there was no association among therapeutic response, pretreatment MHPG level, and clonidine effects on MHPG and blood pressure either prior to or during DMI treatment.

The findings of the study are consistent with the results of previous animal studies that central alpha-2 receptor subsensitivity develops with long-term DMI treatment. However, what is left unanswered and requires further investigation is whether DMI's ability to reduce alpha-2 adrenergic receptor sensitivity is a necessary condition for antidepressant efficacy. The decreased plasma MHPG level during DMI treatment suggests that the reduced NE turnover in the depressed patients studied may reflect the relative balance between the inhibition of NE neuronal firing rate and enhancement of NE released per impulse induced by long-term desipramine treatment. The development of the alpha-2 adrenergic receptor subsensitivity and consequent increased NE release per impulse may be insufficient to overcome the persistently decreased impulse flow.

It has been suggested that a subgroup of depressed patients may have hypersensitive presynaptic alpha-2 adrenergic receptors resulting in decreased synaptic NE and neuronal transmission (Leckman et al. 1980; Charney et al. 1981a). To evaluate this hypothesis, the effects of clonidine on plasma-free MHPG and blood pressure were evaluated in 15 depressed patients and 12 healthy subjects of similar age and sex (Charney et al. 1982b). Following placebo clonidine, the increase in plasma-free MHPG in the controls was significantly greater than the small decrease in the patients ($+0.7$ vs. -0.1 ng/ml, $p < .05$). In addition, the decrease in plasma-free MHPG in the patients following active clonidine was significantly greater than the response to active clonidine in the controls (-0.9 vs. $+0.1$ ng/ml, $p < .01$). However, of central importance is the finding that there was no significant difference between the patients and the controls in the overall "net" effect of clonidine on plasma-free MHPG (i.e., when the effect of placebo clonidine is subtracted from the active clonidine effect the controls had a "net" clonidine induced decrease of 0.6 ng/ml while in the patients there was a "net" decrease of 0.8 ng/ml, a nonsignificant difference). The decreases in blood pressure induced by clonidine were not different between the healthy subjects and the depressed patients.

The findings of this study did not provide support for the hypothesis that depressed patients have hypersensitive presynaptic alpha-2 adrenergic receptors. The ability of clonidine to decrease NE turnover was not different in depressed patients and healthy controls similar in age and sex.

In addition, clonidine induced similar decreases in blood pressure in both groups. This study did reveal several potentially important differences in NE function between the depressed patients and the healthy controls. When considered separately, the plasma-free MHPG response to placebo clonidine and active clonidine were significantly different between the two groups. One explanation for the different MHPG responses of depressed patients and healthy subjects to placebo and clonidine are that the two groups differ in the circadian secretion of MHPG. Wehr et al. (1980) reported that depressed patients were phase advanced in their urinary MHPG circadian rhythm compared to normal subjects. Therefore, in the present investigation, while the plasma MHPG levels of the healthy subjects are rising during the time period of the test day (8 a.m. to 3 p.m.), the MHPG levels of the patients may have peaked earlier and then remained stable. Clonidine simply lowered plasma MHPG an equal amount in both groups. The differences in diurnal MHPG secretion may reflect abnormalities in NE synthesis or metabolism or in the sensitivity of other receptors aside from the presynaptic alpha-2 adrenergic receptor.

Studies are now in progress in healthy subjects and depressed patients before and during AD treatment to determine whether the same assessment of alpha-2 adrenergic receptor sensitivity obtained with clonidine is also observed with yohimbine.

Postsynaptic Alpha-2 Adrenergic Receptors

The ability of clonidine to increase growth hormone secretion appears to be due to stimulation of postsynaptic alpha-2 adrenergic receptors in the hypothalamus (Terry & Martin 1981). Several groups of investigators (Charney et al. 1982b; Checkley et al. 1981; Mattusek et al. 1980) have demonstrated that oral and intravenous clonidine results in significant increases in growth hormone secretion in healthy subjects. These findings indicate that this effect of clonidine may be used as an index of postsynaptic alpha-2 adrenergic receptor function. The growth hormone response to clonidine has been shown to be blunted in drug-free depressed patients compared to healthy subjects, suggesting that the sensitivity of postsynaptic alpha-2 adrenergic receptors may be decreased (Charney et al. 1982b; Checkley et al. 1981; Mattusek et al. 1980). The effect of DMI and amitriptyline on the growth hormone response to clonidine was studied in 12 depressed patients to determine whether the blunted pretreatment response normalized following long-term treatment (Charney, et al., in press-b). The AD treatments did not alter the growth hormone response to clonidine in either treatment responders or nonresponders. Thus, while the etiologic significance of the blunted pretreatment growth hormone response remains to be determined, it does not appear that the efficacy of AD agents is dependent upon increasing the sensitivity of the postsynaptic alpha-2 adrenergic receptors.

Postsynaptic Serotonin Receptors

Despite the evidence that serotonin (5-HT) containing neurons in the central nervous system are involved in the regulation of a variety of brain functions, few paradigms have been developed that are capable of assessing brain 5-HT function in human subjects. In order to develop a method capable of evaluating central 5-HT function, the effects of intravenous tryptophan (6-7 grams) administered over 20 minutes on the secretion of prolactin, growth hormone, and mood state were studied in 10 healthy subjects (Charney et al. in press-a). The tryptophan infusion induced robust increase in prolactin in all 10 subjects with a peak occurring 60 minutes after the start of the infusion. Prolactin levels increased from a baseline of 9.6 +/- 1.4 ng/ml to a peak of 32.6 +/- 6.3 ng/ml ($p < .01$). A significant but variable increase in growth hormone concentration was observed, with the peak increase also occurring 60 minutes following the infusion (1.0 +/- .3 to 12.1 +/- 6.0 ng/ml, $p < .01$). The subjects reported feeling significantly more 'high,' 'mellow,' and 'drowsy' following the infusion in comparison to placebo ($p < .01$). These results, considered in conjunction with animal studies demonstrating that the ability of 5-HT to increase prolactin is potentiated by treatments which increase postsynaptic 5-HT sensitivity (Kuhn et al. 1981), suggest that study of the effects of intravenous tryptophan may be a means of assessing central postsynaptic 5-HT receptor function

in depressed humans. Studies are now in progress in patients to determine the effects of a variety of AD treatments on the actions of intravenous tryptophan.

Treatment Approaches Based Upon the Receptor Sensitivity Model of Antidepressant Action

The identification of changes in postsynaptic beta, alpha-1, and 5-HT receptor function has proven useful in the development of new treatment strategies (Table). It has been suggested that the decrease in beta adrenergic receptor density induced by long-term AD administration may be a good screening test for AD activity. Two recent reports indicate an accelerated development of beta adrenergic receptor subsensitivity when desipramine is combined with the alpha adrenergic antagonists phenoxybenzamine and yohimbine (Paul & Crews 1980; Ursillo et al. 1980). If beta receptor binding alterations are related to AD efficacy, one might expect the clinical response to such a combination to be accelerated. To test this hypothesis, an ongoing investigation is evaluating the therapeutic effects of a yohimbine-desipramine and a yohimbine-amitriptyline combination in depressed patients. The preliminary findings of this study indicate that these combinations can be given safely to human subjects and should provide a valid assessment of the role of beta adrenergic receptor changes in the therapeutic actions of AD agents.

Table

Therapeutic Implications of Receptor Sensitivity Model

Antidepressant-Induced Receptor Alteration	Treatment Strategy*
Decreased beta adrenergic receptor sensitivity	Yohimbine-antidepressant combination
Increased alpha-1 adrenergic receptor sensitivity	Thyroid hormone-antidepressant combination
Increased 5-HT receptor sensitivity	Lithium-antidepressant combination

*See text for details.

A similar approach of attempting to enhance the AD-induced receptor changes has recently been exploited. In a recent report, deMontigny et al. (1981) described eight patients with major unipolar depressions who failed to respond to AD treatment. All eight patients had a marked reduction in symptoms within 48 hours after lithium carbonate was added to their AD regimen. The remarkable improvement in the eight patients was attributed to an enhancement by lithium of central 5-HT systems that acted synergistically with the AD-induced sensitization of 5-HT postsynaptic receptors. To replicate and extend these findings, a placebo-controlled, double-blind investigation of the ability of lithium to potentiate the effects of a variety of AD drugs in treatment refractory patients has recently been conducted (Heninger & Charney, submitted for publication). The results of this study, while strongly supporting the original findings of deMontigny et al. (1981), indicate the therapeutic activity of lithium is not universal, and in some patients this effect may begin to appear only after a minimum of 4 to 7 days of lithium treatment. Clearly, more studies are needed to answer the questions: What type of patients respond most favorably to lithium potentiation? When is the best time to add lithium to an ongoing AD regimen? How long must lithium be continued to maintain a therapeutic response?

The ability of thyroid hormone to accelerate and potentiate the effects of a variety of tricyclic antidepressants has recently received renewed attention (Goodwin et al. 1982). This effect of thyroid hormone may be due to increased sensitivity of alpha-1 adrenergic receptors. Recent animal investigations indicate that thyroid hormone increases the number of alpha-1 adrenergic receptor binding sites in the cerebral cortex (Grob et al. 1981) and the behavioral responses to central postsynaptic alpha adrenergic receptor stimulation (Strombom et al. 1977).

The monoamine receptor sensitivity hypothesis provides a heuristic framework from which to develop clinical research strategies in depressed patients that may generate new insights into the pathophysiologic processes of depressive illness and to the development of improved therapeutic agents. The results decribed above are evidence of this and illustrate the benefits that occur when findings from basic neuroscience are applied to clinical treatment.

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Protein Phosphorylation and Synaptic Mechanisms

Chair: Walter M. Lovenberg, Ph.D.
Hypertension Endocrine Branch
National Heart and Lung Institute
Bethesda, Maryland

Introductory Comments

Walter Lovenberg, Ph.D.[1]

Protein phosphorylations appear to play key roles in neurotransmission and the response of cells to neurotransmitters. A number of protein kinases have been identified in brain and these are known to phosphorylate proteins in several subcellular elements. There appear to be three basic types of protein kinases (cyclic nucleotide dependent, Ca^{+2}-calmodulin dependent, and Ca^{++}-cyclic nucleotide independent) although each of these may exist in various molecular forms. The fact that at least some of the kinases appear to be activated by limited proteolysis tends to make exact characterization of these enzymes difficult. The second messengers cAMP and Ca^{++} are ideally suited for interneuronal communication, since Ca^{++} fluxes are an integral part of neuronal transmission and neuronal membranes are rich in adenylate cyclase. It would appear that at least in certain instances these adenylate cyclases are coupled to neurotransmitter receptors.

Phosphorylation of Cell Membranes. If one incubates synaptic plasma membranes purified from rat brain with Mg^{++} and adenosine triphosphate (ATP) labeled with ^{32}P, a number of protein bands resolved on slab gel electrophoresis are labeled. Autoradiographs of the proteins solubilized from such an incubation indicate that these proteins range in molecular weight from 40K to over 100K. Addition of cAMP to the phosphorylation reaction results in an increase in incorporation of PO_4 into selective bands. Particularly prominent are two bands with molecular weights in the range of about 80,000. These protein stubstrates have been extensively characterized be Greengard and his colleagues (Ueda & Greengard 1977) and were originally termed protein Ia and Ib. More recently they have been localized primarily to synaptic vesicles, and it has been suggested that they be called synapsin. Calcium also stimulates the incorporation of ^{32}P into a number of specific proteins in the presence of calmodulin. Protein I is also a substrate for the Ca^{++}-calmodulin dependent protein kinase. It would appear that each of the kinases act at specific sites (Huttner & Greengard 1979).

The physiologic role for phosphorylation of neuronal specific membrane proteins remains to be defined, although changes in ion permeability, receptor function, and neurotransmitter release are likely candidates.

Cytosolic Phosphorylation. Some of the functions of cytosolic protein kinases have been well defined. In many instances these kinases are involved in regulating the activity of cytosolic enzymes. The regulation of phosphorylase by protein kinase has been well studied. Studies in our laboratory and others indicate that the synthesis of the catecholamines and serotonin may be

[1]Section on Biochemical Pharmacology, Hypertension-Endocrine Branch, National Heart, Lung, and Blood Institute, Bethesda, MD 20205.

regulated by phosphorylation of their biosynthetic enzymes. Both Ca^{++} and cAMP-dependent kinases play important roles in these systems.

With regard to tyrosine hydroxylase, we initially showed that the enzyme could be activated in the presence of a cAMP-dependent protein kinase and protein phosphorylating conditions. This activation at pH 6.0, the pH optimum of the enzymic reaction, appeared to be due to an increased affinity for the cosubstrate, tetrahydrobiopterin, and a decreased affinity for the end-product (dopamine). To understand whether protein phosphorylation represented a significant physiologic control mechanism, it seems important to know the relative concentration of tyrosine hydroxylase and its cosubstrates within the neuron. Also, knowledge of the kinetic properties of the enzyme at a physiological pH was necessary. By a variety of techniques with specific brain lesioning and enzyme kinetics we have been able to suggest a model for the regulation of dopamine synthesis in a dopamine neuron (Levine et al. 1981). By estimating the concentration of enzyme subunits and hydroxylase cofactor concentration in the terminal to be about 100 μM each, and by understanding the kinetics of the phosphorylated and non-phosphorylated enzyme at physiologic pH, we can conclude that a cyclic AMP-dependent phosphorylation of tyrosine hydroxylase converts an essentially inactive enzyme to a fully active form.

Protein phosphorylation may also play an important role in the regulation of tryptophan hydroxylase. We know far less about this system which is specifically present in serotonergic neurons. In contrast to tyrosine hydroxylase this enzyme can only be activated by Ca^{++} calmodulin-dependent protein kinase (Kuhn et al. 1980). At this stage little is known about the regulation of tryptophan hydroxylase *in vivo*, altough protein phosphorylation is likely involved.

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The Possible Role of Phosphorylation of Tyrosine Hydroxylase in Catecholaminergic Neurons[1]

Mitchell A. Lazar, Ph.D., M.D.,[2] and Jack D. Barchas, M.D.[2]

Tyrosine hydroxylase (TH) catalyzes the rate-determining step in the biosynthesis of catecholamines (Levitt et al. 1965). The regulation of TH activity is therefore a major determinant of the quantitative aspects of catecholaminergic neurotransmission. TH can be phosphorylated by cAMP-dependent (Edelman et al. 1981; Joh et al. 1978; Markey et al. 1980; Vulliet et al. 1980), and independent (Raese et al. 1979; Yamauchi & Fujisawa 1981), protein kinases, resulting in kinetic activation of the enzyme. It has been proposed that *in vivo* activation of TH during conditions of increased neuronal firing rate may be mediated by phosphorylation of the enzyme (Weiner et al. 1978; Lazar et al. 1981a). The adequacy of phosphorylation of TH for the short-term control of catecholamine synthesis is the subject of the present paper. A hypothesis concerning the role of TH phosphorylation in neuronal homeostasis is also presented.

Studies of purified bovine striatal TH have elucidated the kinetic properties of the non-phosphorylated and phosphorylated forms of the enzyme (Lazar et al. in press). At representative

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[2]Nancy Pritzker Laboratory of Behavioral Neurochemistry, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA 94305.

concentrations of dopamine and BH_4, K_m, K_i, and V_{max} values of TH at pH 7.0 can be used to theoretically calculate the relative activities of nonphosphorylated and phosphorylated TH in a dopaminergic neuron (Lazar 1980). Such calculations are tabulated in the Table.

Table

Calculations of TH Activity at Different Co-Factor and Inhibitor Concentrations

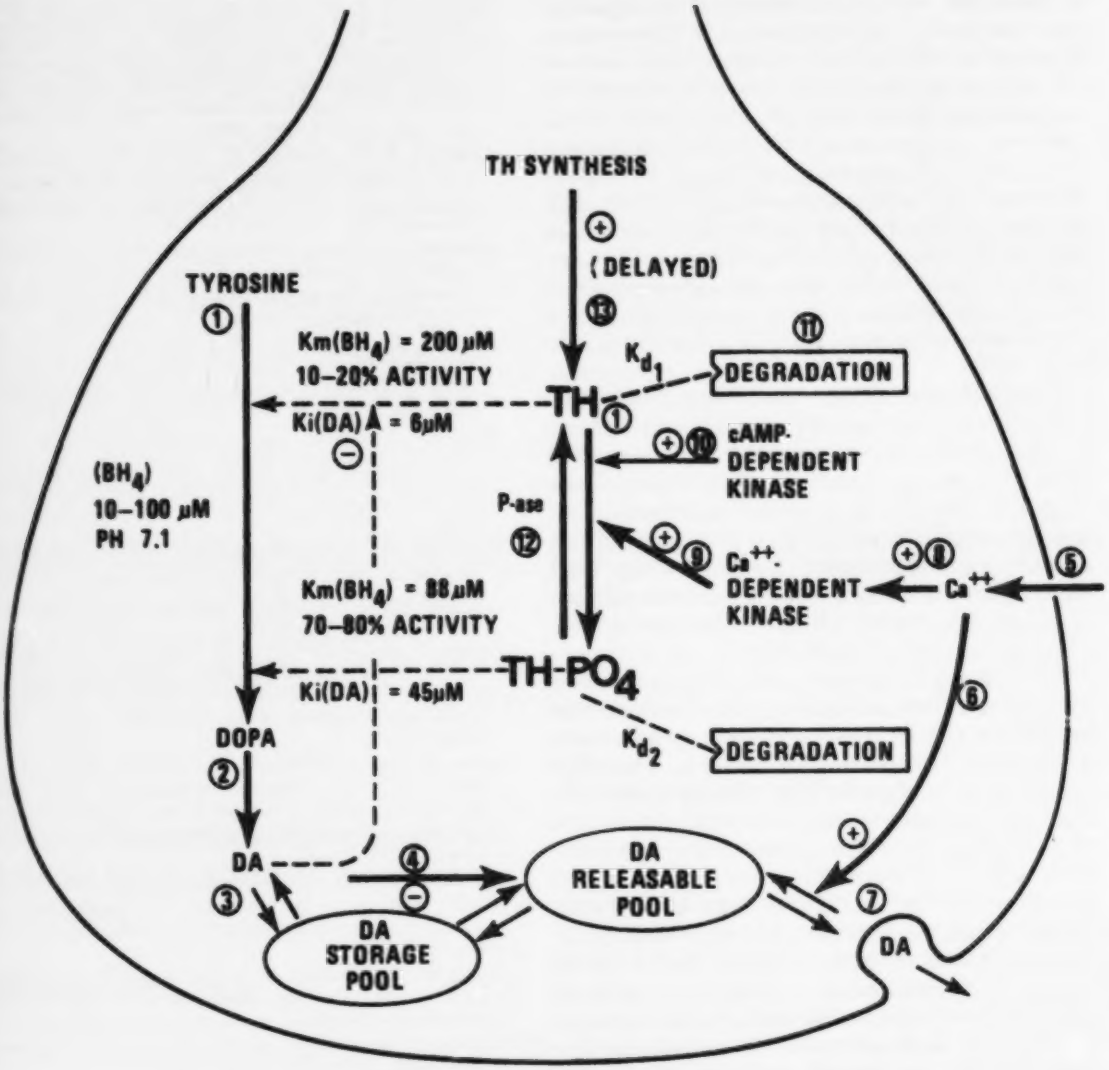
(BH_4)	(Dopamine)	V(Non-P)	V(Phos)	Fold Activation
1	5	0.01	0.15	15.0
10	5	0.11	1.36	12.8
100	5	0.86	7.32	8.5
1	20	0.005	0.11	23.9
10	20	0.05	1.07	21.4
100	20	0.41	6.38	15.6
1	40	0.003	0.09	33.8
10	40	0.03	0.83	27.7
100	40	0.24	5.45	22.7

(BH_4) and (Dopamine) are in μM. V(Velocity) is in nmoles DOPA formed per minute per milligram TH. V(non-P) and V(Phos) refer to calculated rates of reactions catalyzed by nonphosphorylated and phosphorylated TH, respectively. Estimates of BH_4 concentration are from Lloyd and Weiner (1970) and Levine, Kuhn, and Lovenberg (1979). Estimates of dopamine concentration are from Mefford, Gilber, and Barchas (1980), and the range shown takes into account the fact that only about 40% of neuronal dopamine is bound to sedimentable material (Whittaker 1966). Intraneuronal pH has been estimated to be approximately 7.1 by Vigny, Huitorel, Henry, and Pantaloni (1980).

It can be seen that in the range of likely intracellular concentrations of dopamine and BH_4, activation of TH by phosphorylation would be on the order of 8-33 fold, if all TH molecules were phosphorylated. This would be expected to cause a major increase in the rate of catecholamine synthesis, but nevertheless some time would be necessary before the increase in catecholamine synthesis had an effect on the absolute concentration of dopamine concentration within the nerve ending. Thus it is doubtful that the function of increased dopamine synthesis is to replenish the cell with the amount of catecholamine lost during neurotransmission. Yet, it appears that short-term activation of TH occurs during periods of nerve firing, and that this activation is quantitatively similar to the activation induced by phosphorylation of the TH molecule (Masserano & Weiner 1979). The physiological relevance of TH phosphorylation may relate to the observations that newly synthesized catecholamines, including norepinephrine (Kopin et al. 1968) and dopamine (Glowinski 1970), are preferentially released during nerve stimulation.

A dopaminergic nerve terminal is schematically represented in the Figure. Numbers in parenthesis in the text refer to the correspondingly numbered steps in the Figure. Kinetic properties of purified bovine striatal TH, which were used to generate the calculation in the Table, are shown in the Figure (Lazar et al. 1982). It is proposed that phosphorylation would increase the rate of DOPA formation as discussed above (1). As TH is the rate-limiting step in catecholamine synthesis, immediate decarboxylation of DOPA (2) would result in an increased rate of dopamine synthesis. Dopamine exists in three intracellular forms, which may or may not be experimentally indistinguishable: a) cytoplasmic, which serves to inhibit TH, b) stored, not for immediate release (3), and c) available for release (4). Presumable in times of active nerve firing more newly synthesized dopamine is channeled to the releasable pool than in times of relative inactivity.

Intracellular calcium increases as a result of nerve stimulation (5). Calcium (6) is absolutely required for release of transmitter (7). In addition, calcium influx has also been shown to result in activation of a Ca^{+2}-dependent protein kinase (8), possibly via calmodulin (Schulman & Greengard 1978). Calcium-dependent protein phosphorylation has been speculated to play a role in transmitter release (DeLorenzo et al. 1979). It is hypothesized here that calcium-dependent phosphorylation may be involved in TH activation *in vivo* (9). Raese et al. (1979) have shown that cyclic AMP-independent protein kinase may also activate TH, and it has been recently suggested that calcium-dependent phosphorylation may also activate the enzyme (Yamauchi & Fujisawa 1980). If this were the case in vivo, calcium-dependent phosphorylation would promote both the increased release of neurotransmitter and the increased synthesis of transmitter available for release. Thus one intracellular event, the increase in calcium concentration, may rapidly result in neurotransmitter synthesis and neurotransmission, with little compromise of the cell's ability to respond to further stimuli. Phosphorylation of TH by cAMP-dependent protein kinase (10) may also serve a physiological role as a parallel method of increasing catecholamine synthesis.



HYPOTHESIZED ROLE OF PHOSPHORYLATION IN THE REGULATION OF TYROSINE HYDROXYLASE ACTIVITY DURING STIMULI RESULTING IN INCREASED NEURONAL FIRING RATE

FIGURE. Schematic dopaminergic neuron. Numbered steps are referred to in text. Pluses and minuses refer to activating and inhibiting steps, respectively. The activities shown for phosphorylated (TH-PO_4) and non-phosphorylated TH refer to the ratio of TH activity at pH 7to that at pH 6.0, the *in vitro* pH optimum of non-phosphorylated TH. Estimates of dopamine, BH_4, and hydrogen ion concentrations are derived from the references to the Table.

Once TH is activated there are two hypothesized mechanism of inactivation of the enzyme. Thermal stability of the phosphorylated form of the enzyme is significantly less than that of the nonphosphorylated form of TH (Lazar et al. 1981b). If this correlates with *in vivo* turnover rate (Bond 1975), phosphorylated TH may be degraded faster than nonphosphorylated TH (11, Kd_2 greater than Kd_1). This could serve to time limit the activation process. In addition, phosphorylated TH may be susceptible to dephosphorylation (12), possibly by a phosphatase with some specificity for TH (Lazar et al. 1978).

If degradation of TH is involved in the regulation of levels of phosphorylated TH, then after a number of stimuli there might be depletion of TH molecules. However, there is ample evidence that long-term stimulation produces induction of TH synthesis in the cell body (13), possibly by transsynaptic induction (Thoenen 1975). Thus there exists a mechanism to increase the number of nonphosphorylated TH molecules after periods of sustained nerve stimulation.

In summary, phosphorylation produces a number of significant kinetic changes in TH. The phosphorylated form of the enzyme appears more suited to the intraneuronal milieu than is the nonphosphorylated form of TH. This magnifies the effect of phosphorylation of TH on *in vivo* catecholamine synthesis. The relative inhibition of nonphosphorylated TH under physiological constraints is what may enable the cell to regulate catecholamine synthesis quickly with relatively little overall change in the internal milieu. If, as suggested, calcium influx and calcium-dependent phosphorylation link nerve stimulation, transmitter release, and synthesis of transmitter for release, then the phosphorylation of tyrosine hydroxylase may play a crucial homeostatic role in the regulation of catecholaminergic neurons.

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Calcium-Dependent Phosphorylation and the Regulation of Serotonin Synthesis

Donald M. Kuhn, Ph.D.[1]

Introduction

The brain is a major organ system which is comprised of over 10 billion heterogenous cells and driven by over 300 trillion connections and interconnections among these cells. Dysfunction of the brain presents a difficult problem in diagnosis and treatment. Not surprisingly, *brain* dysfunction manifests itself in many ways along a broad continuum of psychiatric disorders, most of which remain poorly understood. However, the results of a great deal of research are providing clues into the etiology of some psychiatric illnesses. A major focus for much research into psychiatric disorders centers on the chemistry of the neurotransmitter systems and one such neurotransmitter, serotonin (5-HT), is the subject of the present discussion. The reader only has to examine this volume to realize that 5-HT is still implicated in a variety of psychiatric disorders, not the least of which include depression and schizophrenia. This chapter will concentrate on the control of 5-HT synthesis and the role of phosphorylating mechanisms in this process.

The biosynthetic pathway for 5-HT begins with the conversion of the essential amino acid l-tryptophan (TRY) to 5-hydroxytryptophan (5-HTP) and is completed by the decarboxylation of 5-HTP (by l-aromatic amino acid decarboxylases) to 5-HT. The first step, TRY→ 5-HTP, is catalyzed by tryptophan hydroxylase which is also the rate limiting step in 5-HT synthesis, and this reaction takes place exclusively in a very small proportion of cells in the brain. This is known as the 5-HT neuronal system. Since tryptophan hydroxylation is the initial and rate limiting step in 5-HT synthesis, the rate of this reaction can have a profound influence on the amount of 5-HT produced. Therefore, the present discussion will deal exclusively with the control of tryptophan hydroxylase activity. Furthermore, the role of phosphorylation in controlling 5-HT synthesis will focus, by necessity, on the rate-limiting hydroxylation step. These restrictions by no means lessen the importance of numerous other aspects of 5-HT synthesis and control (e.g., levels of substrates, release or uptake of 5-HT, 5-HT receptors) nor do they indicate that a phosphorylation reaction is the only means by which tryptophan hydroxylase is controlled.

Phosphorylation reactions are mediated by protein kinase enzymes which, in general, involve the transfer of the terminal phosphate from adenosine triphosphate (ATP) to some substrate (e.g., another enzyme or protein) via a covalent linkage. Perhaps the most extensively studied protein kinases are the ones which are dependent on cyclic nucleotides (cAMP or cGMP) for activity whereas, more recently, a number of protein kinases have been discovered to be dependent on calmodulin (CaM), the calcium-binding protein

[1]Section on Biochemical Pharmacology, Hypertension-Endocrine Branch, National Heart, Lung, and Blood Institute, Bethesda, MD 20205.

(*see* Cheung 1980), for expression of catalytic activity. Furthermore, it appears that tryptophan hydroxylase is a substrate for Ca^{2+}-CaM dependent proteins kinase and that phosphorylating conditions activate tryptophan hydroxylase.

Method

Tryptophan hydroxylase was measured in extracts from rat mesencephalic tegmentum, since this brain section contains the majority of all cerebral 5-HT cell bodies and is rich in tryptophan hydroxylase activity. The enzyme was assayed by the fluorometric method described by Baumgarten et al. (1973) which involves the measurement of 5-HTP fluorescence after termination of the enzyme reaction. In order to study the effects of phosphorylation on tryptophan hydroxylase, ATP, Mg^{2+}, and calcium were added to the assay mixture. All reactions were carried out for 15 minutes at 37°C. Additional details on methodology are given in the following sections.

Results and Discussion

Effects of Phosphorylating Conditions on Tryptophan Hydroxylase Activity

Hamon et al. (1978) first observed that tryptophan hydroxylase could be activated by phosphorylating conditions and almost simultaneously Kuhn et al. (1978) reported similar observations. In these studies the addition of 0.5 mM ATP and 5.0 mM Mg^{2+} to the enzyme reaction mixture resulted in increased tryptophan hydroxylase activity when the assays were carried out with subsaturating concentrations of the substrate 2-amino-4-hydroxy-6-methyl-5,6,7,8 tetrahydrobiopterin (6-MPH_4). Lineweaver-Burk plots of kinetic data revealed that phosphorylating conditions decreased the apparent Km of tryptophan hydroxylase for the pteridine cofactor (6-MPH_4) without changing the Km for tryptophan. In fact, the Km for 6-MPH_4 was reduced from 210 to approximately 90 μM by phosphorylating conditions (Kuhn et al. 1978).

The requirements for activation of tryptophan hydroxylase appeared quite simple initially (Hamon et al. 1978; Kuhn et al. 1978). In addition to ATP and Mg^{2+}, only Ca^{2+} was necessary to allow complete activation. The Ca^{2+} requirement is demonstrated in Figure 1. This curve was generated by using a Ca^{2+}-EGTA buffer to control the levels of free Ca^{2+} (which can be calculated) and zero Ca^{2+} simply indicates the addition of excess EGTA without added Ca^{2+}. It can be seen that the reaction is sensitive to low concentrations of Ca^{2+} (10^{-7}–10^{-3} M Ca^{2+}) and the activation reaches half maximum at approximately 7.5×10^{-7} M Ca^{2+}. A number of cyclic nucleotides including CAMP and cGMP were tested and found to be inactive. Thus, the activation of tryptophan hydroxylase by phosphorylating conditions was apparently mediated by a cyclic nucleotide-independent but Ca^{2+}-dependent protein kinase. This total dependency on Ca^{2+} suggested that CaM might also be involved and the remaining discussion will concentrate on results with CaM and the phosphorylation induced activation of tryptophan hydroxylase. The interested reader is referred to previous, more detailed discussions on this subject (Kuhn et al. 1980).

The role of calmodulin in the activation of tryptophan hydroxylase by phosphorylating conditions. Cheung (1980) has identified several criteria which are

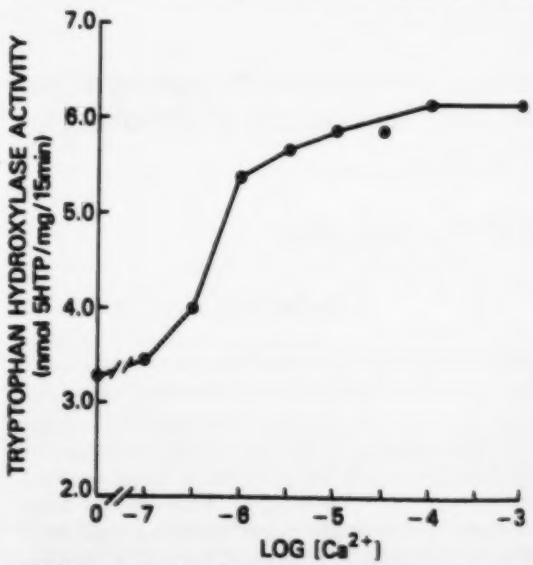

FIGURE 1. Calcium dependency of the activation of tryptophan hydroxylase by phosphorylating conditions. Ca^{2+} concentrations were adjusted to the indicated values by the use of Ca^{2+}-EGTA buffers. Zero Ca^{2+} refers to the use of excess EGTA.

useful in identifying CaM dependent biological reactions and previous studies (*see* above) satisfied one criterion, Ca^{2+} dependency. A second criterion demands that the removal of CaM from the tissue alters the reaction. To test this, tegmental extracts were chromatographed on an affinity matrix comprised of fluphenazine covalently attached to Sepharose 4B (*see* Charbonneau & Cormier, 1979, for a description) in order to remove endogenous CaM. The data in the Table indicate that removal of CaM rendered the hydroxylase unresponsive to phosphorylating conditions. The ability of exogenously added CaM to reinstate the activation in chromatographed brain extracts is also demonstrated in the Table, and these data satisfy another criterion, that CaM can be added back into the system from which it was removed and at the same time restore function to the system. Analysis of brain extracts by SDS-polyacrylamide slab gel electrophoresis both before and after affinity chromatography on fluphenazine Sepharose confirmed that CaM was indeed present in the brain under study (satisfying the fourth criterion of Cheung 1980) and that the affinity chromatography was quite efficient and selective in removing CaM. These results are shown in Figure 2.

A fifth criterion states that fluphenazine should inhibit the CaM-dependent reaction and is based on the observation that fluphenazine and a large number of other antipsychotic drugs bind with high affinity to CaM in a Ca^{2+}-dependent fashion (*see* Weiss et al. 1980). To test this criterion, a number of antipsychotic drugs were added to the tryptophan hydroxylase reaction mixture in the presence of phosphorylating conditions. The effects of three such drugs are shown in Figure 3. It can be seen that increasing concentrations of fluphenazine, trifluoperazine, and cis-flupenthixol produced inhibition of the phosphorylation-induced activation of tryptophan hydroxylase. Other antipsychotics including penfluridol, pimozide, haloperidol, and chlorpromazine were also effective in this regard, the inhibitory potencies for the inhibition of the activation of tryptophan hydroxylase by these drugs agreed precisely with the order of potency of the binding of these drugs to CaM (Weiss et al. 1980). Since these drugs are by no means completely specific in their *in vitro* actions, additional studies were carried out to assess the extent to which their inhibitory properties were related to CaM binding. The

FIGURE 2. SDS-polyacrylamine slab gel electrophoresis of brain protein. Lane A, extract (100 μg of protein) before chromatography on fluphenazine-sepharose 4B; Lane B, effluent (100 μg of protein) from fluphenazine-sepharose 4B; Lane C. EGTA eluant (2 μg of protein) from affinity column after dialysis against 0.1 mM Ca^{2+}; Lane D, purified calmodulin (2 μg) from pig brain acetone powder prepared by the method of Klee (1977). Arrows indicate the position of calmodulin. Reprinted, with permission, from Kuhn et al. (1980).

Table

Phosphorylation Effects on Tryptophan Hydroxylase After Chromatography on Fluphenazine-Sepharose

		Assay Conditions	
Enzyme	Addition	Control	Phosphorylating
Control	-	5.21 ± 0.07	8.44 ± 0.40
Chromatographed	-	5.65 ± 0.21	5.72 ± 0.18
	Calmodulin	5.32 ± 0.04	9.22 ± 0.42
	Calmodulin + EGTA	5.20 ± 0.15	4.82 ± 0.19

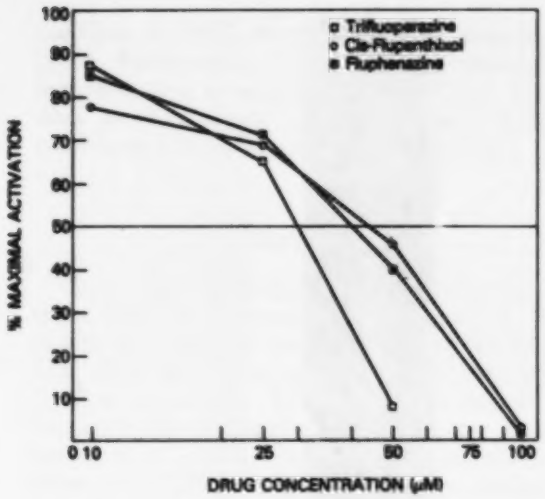

FIGURE 3. Drug-induced inhibition of the effects of phosphorylating conditions on tryptophan hydroxylase. Drugs were added in the final concentrations listed on the abscissa. Drugs used were: ■, fluphenazine; □, trifluoperazine; O, cis-flupenthixol. Data are expressed as percent maximal activation, calcualted by dividing the activity under phosphorylating conditions in the absence of drug. Reprinted, with permission, from Kuhn et al. 1980.

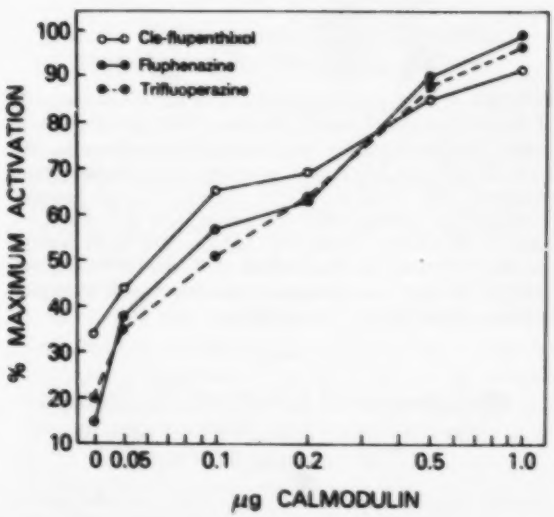

FIGURE 4. Protection against drug-induced inhibition of phosphorylation of tryptophan hydroxylase by calmodulin. Phosphorylation reaction mixtures were prepared and cis-flupenthixol (O-O), fluphenzaine (•—•) or trifluoperazine (•--•) was added to the reaction mixture. Reprinted, with permission, from Kuhn et al. (1980).

results in Figure 4 indicate that the addition of exogenous CaM to reaction mixtures containing fluphenazine, trifluoperazine, or cis-flupenthixol (50 μM for each) overcame the inhibitory effects of these drugs. Thus, it seems likely that the inhibitory effects of these drugs are mediated by their ability to bind to CaM.

A final criterion suggests that antibodies to CaM should prevent the CaM-dependent process but, unfortunately, this criterion has not yet been fulfilled. The assay for tryptophan hydroxylase requires the presence of a reducing agent, typically dithiothreitol (DTT), and DTT reduces the sulfhydryl bridge which retains structural integrity (and function) between the heavy and light chains of the IgG antibody raised against CaM. Experiments are continuing with various CaM antibody preparations to test their ability to block the CaM dependent activation of tryptophan hydroxylase.

In summary, the data suggest rather conclusively that CaM is an essential component in the activation of tryptophan hydroxylase by phosphorylating conditions. However, some very important questions have not yet been answered. For example, is tryptophan hydroxylase itself directly phosphorylated during activation or is some other protein intermediate the substrate for the CaM-dependent protein kinase? Only studies with highly purified preparations of tryptophan hydroxylase will allow this question to be answered and unfortunately, such a purified enzyme preparation is not yet available. Another question which must be answered is whether this phosphorylation-induced activation occurs *in vivo*. Fortunately, some data are available which are pertinent to this question. For example, tryptophan hydroxylase in brain slices is activated by neuronal depolarizing conditions in a Ca^{2+} dependent manner and this activation can be blocked by fluphenazine (Mestikevay et al. 1982; Boadle-Biber 1982). Furthermore, the cerebral distribution of the Ca^{2+} -CaM dependent protein kinase parallels that of tryptophan hydroxylase (Hamon et al. 1979), and selective destruction of 5-HT cells with the neurotoxin 5,7-dihydroxytryptamine also substantially reduces Ca^{2+} dependent protein kinase activity (Hamon et al. 1979). Finally, Yamauchi and Fujisawa (1980) have identified three different CaM-activated protein kinases in brain, and tryptophan hydroxylase is apparently a substrate for one of these enzymes. Although these data do not constitute conclusive proof, col-

lectively they strongly indicate that a Ca^{2+}-CaM dependent protein kinase can phosphorylate tryptophan hydroxylase *in vivo*, and this mechanism could be closely coupled to neuronal depolarization and Ca^{2+} influx.

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Control of Phosphorylation of a Vesicle-Associated Protein, Synapsin 1[1]

Mary B. Kennedy, Ph.D.[2]

Reversible phosphorylation of proteins, catalyzed by a class of enzymes called protein kinases, has been shown to play a role in regulating a variety of cellular processes. For example, several hormones stimulate the synthesis of cAMP which then acts as a "second messenger," stimulating the phosphorylation of specific proteins by cAMP-dependent protein kinase (Greengard 1978; Krebs & Beavo 1979). In an attempt to understand the mechanism of action of neurotransmitters that have relatively long term effects on neurons, Paul Greengard's laboratory showed that some of these neurotransmitters stimulate the synthesis of cAMP (Greengard 1981). More recently, the same lab has described a protein doublet, initially termed protein I, that is found only in neural tissue, and is phosphorylated by cAMP-dependent protein kinase (Ueda & Greengard 1977). Studies on the location of protein I have shown that it is located specifically in most, if not all, synaptic terminals (Bloom et al. 1979; DeCamilli et al. 1979) where it is associated primarily with synaptic vesicles (Ueda et al. 1979; DeCamilli, Harris, Huttner and Greengard, in preparation). Because of its location, the protein has been renamed synapsin I (Huttner et al. 1981a).

More detailed studies on phosphorylation of synapsin I have shown that its phosphorylation can be regulated by free calcium levels in nerve terminals, as well as by cAMP (Krueger et al. 1977). This was demonstrated in an experiment in which brain synaptosomes were prelabeled with ^{32}P-phosphate, then transferred to depolarizing solutions containing either veratridine or high potassium, in the presence or absence of calcium. Following brief incubations, protein phosphorylation was assessed by SDS gel electrophoresis and

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[2]Division of Biology 216-76, California Institute of Technology, Pasadena, CA 91125.

autoradiography. Depolarization in the presence of calcium, but not in its absence, increased the rate of phosphorylation of synapsin I (Krueger et al. 1977; Sieghart et al. 1979). Three lines of evidence indicate that the calcium-stimulated phosphorylation occurs by a pathway distinct from the cAMP-dependent pathway. First, depolarization of synaptosomes in the presence of calcium produces no measurable increase in cAMP (Krueger et al. 1977). Second, calcium-stimulated phosphorylation occurs at three distinct sites on the synapsin I molecule. One (site 1) is recovered in a 10 kdalton fragment after proteolysis with *Staph aureus* V8 protease and is the same site that is phosphorylated by cAMP-dependent kinase. The other two (sites 2 and 3) are recovered in a 30 kdalton fragment and are not phosphorylated by cAMP-dependent protein kinase under physiological conditions (Huttner & Greengard 1979; Huttner et al. 1981b). Finally, calcium and calmodulin-dependent protein kinase activity has been identified in synaptosomal lysates (Schulman & Greengard 1978a,b).

In order to purify and characterize the calcium-dependent protein kinase or kinases that phosphorylate synapsin I, a quantitative assay for such kinases was developed using purified synapsin I as a substrate (Kennedy & Greengard 1981; Figure). Under optimal conditions in this assay, the rate of phosphorylation of synapsin I by a crude brain homogenate is stimulated as much as 40-fold by calcium ion to a rate of about 5 nmoles/min/mg of protein. Both the soluble and particulate fractions of the homogenate contain calcium-stimulated synapsin I kinase (Figure). The soluble activity catalyzes the phosphorylation of all three sites on synapsin I, while the particulate activity phosphorylates primarily sites 2 and 3 (Kennedy & Greengard 1981). Fractionation of the soluble proteins by DEAE-chromatography revealed the presence of two distinct synapsin I kinases. One peak of activity phosphorylated site 1 ("10 k fragment kinase") while the other, larger, peak phosphorylated sites 2 and 3 ("30 k fragment kinase"). The 10 k fragment kinase is calcium-dependent, but does not at this stage of purification require exogenous calmodulin. It is, however, inhibited by 50 μM trifluoperazine which suggests that it may be calmodulin-dependent, and have a sufficiently high affinity for calmodulin that the two copurify through the DEAE fractionation. The 30 k fragment kinase is both calcium and calmodulin-dependent.

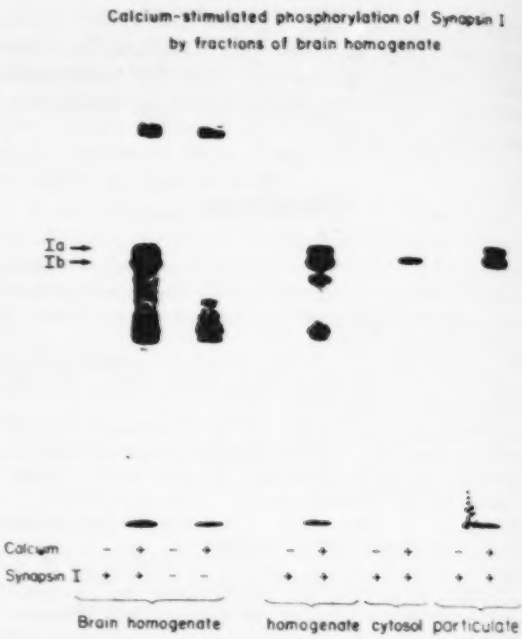

FIGURE. The fractions of brain homogenate were prepared, and assays performed as described in Kennedy and Greengard, 1981.

This latter soluble synapsin I kinase activity is apparently closely related or identical to the particulate calmodulin-dependent synapsin I kinase (Kennedy, McGuinness, and Greengard, manuscript in preparation). Fifty to seventy percent of the particulate enzyme can be solubilized by prolonged incubation in dilute buffer, and can then be partially purified by DEAE-cellulose chromatography. The enzymes of both soluble and particulate origin have been further purified by calmodulin-sepharose affinity chromatography. At this stage of purification, the two enzymes are indistinguishable in their catalytic properties (substrate specificities, affinity for substrates, calcium requirement, optimum pH) and in their mobilities on DEAE-cellulose.

Both of the brain synapsin I kinases can be distinguished from the two previously described calmodulin-dependent protein kinases, myosin light chain kinase (Dabrowska et al. 1978; Yagi et al. 1978) and phosphorylase kinase (Cohen et al. 1978), by differences in their substrate specificities (*see* Table), in their mobilities on DEAE-cellulose, and in their tissue distributions

(Kennedy & Greengard 1981). The calcium-stimulated synapsin I kinase activities are three to ten times more highly concentrated in brain homogenates than in any other tissue homogenates assayed. The relationship of these enzymes to the endogenous particulate calmodulin-dependent protein kinase described by Schulman and Greengard is being investigated.

Table

Comparison of Substrate Specificities of Calmodulin-Dependent Protein Kinases

Enzyme	Substrate		
	Myosin Light Chain	Phosphorylase b	Synapsin I
	pmole/min	pmole/min	pmole/min
Myosin light chain kinase (M. Conti and R. Adelstein)	27	---	5.7 (10 k fragment)
Phosphorylase kinase (J. Wang)	---	14	1.3 (30 k fragment)
Crude synapsin I kinase	1. 2. 0.08	< 0.02	76 89

Purified enzymes were obtained from the indicated investigators. Crude synapsin I kinase refers to the DEAE peak of enzyme activity described in Kennedy and Greengard, 1981. Myosin light chain was a gift of Dr. Angus Nairn. Phosphorylase b was purchased from Sigma Chemical Co. Assays were performed as described in Kennedy and Greengard, 1981. Mixing experiments indicated that the crude synapsin I kinase preparation did not contain substances that interferred with the measurement of either myosin light chain kinase or phosphorylase kinase.

The complex regulation of phosphorylation of synapsin I, together with its association with synaptic vesicles, suggests it is involved in a vesicle function that is regulated by events that alter either cyclic AMP levels or calcium levels. One such function is transmitter release. In some terminals, agents that alter cyclic AMP levels can cause facilitation, which is an increase in the number of quanta of transmitter released per impulse (e.g., Goldberg & Singer 1969; Kandel 1981). In addition, under some circumstances, calcium influx through voltage-dependent calcium channels can lead to post-tetanic potentiation which is a relatively long-lasting increase in the number of quanta released per impulse (Rosenthal 1969). Future experiments should elucidate whether synapsin I is involved in regulation of transmitter release, or in some other vesicle function.

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The Indole Hallucinogens—A New Look at Their Mechanisms of Action

Chair: Herbert Y. Meltzer, M.D.
Department of Psychiatry
University of Chicago
Pritzker School of Medicine
Chicago, Illinois

Action of Hallucinogenic Drugs at Postsynaptic Serotonergic Receptors[1]

Barry L. Jacobs, Ph.D.,[2] James Heym, Ph.D.,[2] and Kurt Rasmussen, B.S.[2]

Hallucinogenic drugs such as LSD, psilocin, 2,5-dimethoxy-4-methylamphetamine (DOM), mescaline, and N,N-dimethyltryptamine (DMT) appear to constitute a distinct drug class based on their similar phenomenological effects in humans and the fact that cross-tolerance can be demonstrated between many of them. Theories regarding the mechanism of action of these drugs have gone through several distinct phases, all of them focusing on the role of serotonin. In the initial phase, in the mid-1950s, LSD was hypothesized to exert its psychological actions by blocking serotonin's synaptic effect. These conclusions, however, were based exclusively on pharmacological studies of LSD's action in the periphery, and were soon criticized. Following this, in the early 1960s, the emphasis shifted to an effect upon serotonin in the central nervous system (CNS), but without regard to the precise site of action, i.e., presynaptic or postsynaptic. In the mid-1960s, studies employing fluorescence histochemistry delineated the localization of serotonin-containing neurons within the CNS, their projection pathways, and their axon terminal distribution. This information provided the foundation for theories in the 1970s which proposed that the effects of LSD and related hallucinogens were mediated specifically by an action upon the cell bodies of serotonergic neurons (hereafter referred to as the "presynaptic" effect). Finally, in the fourth phase, emphasis has switched to the action of hallucinogenic drugs directly upon the target neurons of serotonergic projections (hereafter referred to as the "postsynaptic" effect). The data supporting this latest concept, which have been gathered primarily within the last few years, will be the subject of this brief review. Because of space limitations, many of the issues discussed will be either minimally referenced or unreferenced. For more detailed information, the reader is referred to two recent reviews (Jacobs & Trulson 1981; Jacobs, in press).

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[2]Program in Neuroscience, Department of Psychology, Princeton University, Princeton, NJ 08544.

The authors will first describe the presynaptic model. This will provide a more meaningful and appropriate context in which to discuss the postsynaptic model, as well as afford the opportunity to compare and contrast the two models.

Based on previous neurochemical data which indicated that LSD decreased serotonin turnover, Aghajanian and his co-workers reasoned that this might be mediated by a decrease in the unit activity of serotonergic neurons. They therefore set out to test this directly be examining the effects of systemic administration of LSD on unit activity of brain serotonergic neurons in the chloral hydrate anesthetized rat (Aghajanian et al. 1968). They lowered tungsten microelectrodes into the brain area with the densest aggregation of serotonergic neurons, the midbrain dorsal and median raphe nuclei, and observed the slow (1-2 spikes/sec) and regular discharge pattern that appears to characterize all serotonergic neurons in brain. When LSD was then administered intravenously, a dose of 25-50 μg/kg was sufficient to cause a complete suppression of activity. By contrast, none of the neurons outside of the raphe ceased firing in response to the drug. An important control experiment in this series demonstrated that, unlike LSD, brom-LSD exerted virtually no effect on serotonergic neurons in doses of 25-50 μg/kg. These same investigators went on to test the effects of a variety of systemically administered psychoactive drugs, including several hallucinogens (Aghajanian et al. 1970). They reported that DMT produced an effect very similar to that of LSD, but at significantly higher doses (approximately 700 μg/kg). Interestingly, mescaline and DOM depressed the activity of only a subgroup of midbrain raphe neurons, those in the ventral portion of the dorsal nucleus. Atropine, scopolamine, phencyclidine, and chlorpromazine were essentially without effect on serotonergic unit activity. In separate studies, Aghajanian's group also showed that psilocin was effective in depressing serotonergic unit activity, whereas amphetamine consistently increased the activity of these cells. Finally, an experiment from the authors' laboratory indicated that low doses (20 μg/kg, i.v.) of the hallucinogen 5MeODMT also exerted a potent depressant effect on the activity of serotonergic neurons (Mosko & Jacobs 1977).

The next issue was to determine whether LSD and related hallucinogens exerted their depressant effects directly on serotonergic neurons, or whether this action was mediated indirectly, perhaps by some type of feedback loop. The most straightforward approach to this question involved the direct application of LSD, psilocin, DMT, 5MeODMT, and mescaline onto neurons in the area of the dorsal raphe nucleus by means of microiontophoresis. In all cases, excluding those experiments with mescaline, the iontophoretic application of the hallucinogenic drugs produced a profound suppression of serotonergic unit activity at low ejection currents (Haigler & Aghajanian 1973; Aghajanian & Haigler 1975). This supported the hypothesis that the effect of hallucinogenic drugs is mediated by a direct action upon serotonergic neurons, possibly one mediated by serotonin receptors. Since the iontophoretic application of mescaline failed to depress serotonergic unit activity, even in the subset of those cells that were affected by systemic administration, it was concluded that unlike the other hallucinogens, mescaline's effect on serotonergic neurons is mediated indirectly.

A final, very important issue remained to be resolved. If the action of hallucinogenic drugs is mediated by a depressant action on serotonin-containing neurons, why then are not compounds such as l-5-hydroxytryptophan (5-HTP) and l-tryptophan, both of which depress raphe unit activity, hallucinogenic? The answer, at least in the context of this theoretical framework, is contained in two elegant experiments by Haigler and Aghajanian (1973, 1974). When serotonin is iontophoretically applied onto serotonergic neurons in the raphe nuclei and onto their postsynaptic target neurons in the ventral lateral geniculate or amygdala, it is approximately equipotent in depressing unit activity at these various sites. Contrary to this, when LSD or psilocin is tested in the same manner, it has a much more profound effect on the serotonergic cells than on their target neurons. In other words, hallucinogenic drugs have an action that appears to be *preferential* for serotonin-containing neurons. Thus, it is reasoned, when brain levels of serotonin are elevated by administration of its precursors 1-5-HTP or l-tryptophan (or any of a variety of other pharmacologic means), serotonergic unit activity is depressed, but so is the activity of target neurons receiving serotonergic inputs. On the other hand, when LSD is administered systemically, it acts to depress serotonergic unit activity, while having

little direct effect on target neurons. Because much of serotonin's action on target neurons in the forebrain is inhibitory, it is hypothesized that the ultimate effect of LSD's preferentially depressant action on serotonergic neurons is to produce a disinhibition of target neurons, which is precisely the opposite of the depression produced by elevated synaptic levels of serotonin.

Since this disinhibition will be manifested most impressively in those areas with the densest aggregation of serotonin axon terminals, i.e., portions of the visual system and limbic system, an obvious neuronal model is available to account for two of the major aspects of hallucinogenic drug action: visual hallucinations and alterations of affect. This, then, is the presynaptic serotonergic model of hallucinogenic drug action. It is based on several assumptions: 1) All hallucinogenic drugs strongly depress the activity of at least some group of serotonergic neurons. 2) Serotonin's synaptic action in the forebrain is strictly inhibitory. 3) Hallucinogenic drugs exert little direct effect on postsynaptic serotonergic receptors. There is now reason to question the validity of all three of these assumptions, however, in this review, focus will be on only the first and the third.

All of the electrophysiological studies described above were conducted in anesthetized and/or immobilized animals, thus making it impossible to relate changes in unit activity produced by hallucinogenic drugs to changes in behavior. If our ultimate goal is to draw conclusions about functional relationships, such analyses are imperative. In an attempt to provide a more stringent test of the presynaptic model of hallucinogenic drug action, the authors decided to administer these drugs to awake freely moving cats and to study changes in the activity of brain serotonergic neurons concomitantly with changes in behavior. In order to analyze the behavioral effects of the hallucinogens, they employed an observational method of scoring changes in the spontaneous occurrence of specific response categories in the cat (Jacobs et al. 1977). In order to record the activity of single units in freely moving cats, they developed a technique that employs bundles of flexible large-tipped microwires (32 or 64 μm diam.) rather than the traditional small-tipped high-impedance metal or glass microelectrodes (Jacobs et al. in press). These bundles of microwires can be advanced through the brain by means of an attached mechanical microdrive. Using this technique, the authors had great success in isolating serotonergic units in various raphe nuclei of the cat brainstem (e.g., dorsalis, centralis superior, and pallidus). This technique also allows them to "hold" cells for long periods of time (from several hours up to several days) and in spite of vigorous movements on the part of the cat.

The authors first describe their experiments with 5-MeODMT, which has a molecularly more simple structure than LSD and produced more clearcut data. They were particularly interested in the temporal correlations between the onset, peak, and offset of the behavioral and unit data, and whether or not the behavioral and unit data would have a correlated dose dependency. In order to examine these issues, they administered 5-MeODMT in doses of 10, 25, 50, 100, or 250 μg/kg intramuscular (i.m.) and monitored the activity of serotonin-containing neurons in the dorsal raphe nucleus in conjunction with any gross behavioral effects (Trulson & Jacobs 1979a). Under baseline conditions, serotonergic neurons in the awake freely moving cat discharge with the same characteristic slow rhythmic activity seen in the anesthetized rat. Following injections of 5-MeODMT, serotonergic unit activity was rapidly depressed in a dose-dependent manner, and dose-dependent increases were observed in the rate of limb flicking and abortive grooming. Furthermore, the onset, peak, and offset of the behavioral effects were temporally correlated with the onset, peak, and offset of changes in unit activity. By directly correlating behavioral changes with changes in the activity of serotonin-containing neurons, the authors at the time, felt that this study provided perhaps the strongest direct evidence for the presynaptic serotonin hypothesis of hallucinogenic drug action.

When this approach was extended to the study of LSD, the results were generally similar to those seen with 5-MeODMT, but with two critical differences (Trulson & Jacobs 1979b). First, a 50 μg/kg dose of LSD produced a depression of serotonergic unit activity lasting, on the average, 3-4 hours, while the behavioral effects lasted for at least 6-8 hours. Second, when the 50 μg/kg dose was readministered 24 hours later, it produced little or no behavioral effect (tolerance), but the effect on serotonergic unit activity was as large as

two dissociations of unit activity and behavior, the authors began to question the validity of the presynaptic serotonergic hypothesis.

This skepticism has been bolstered by their more recent experiments with DOM, mescaline, and psilocin (Trulson et al. 1981). With all three drugs, they observed the same temporal dissociations of serotonergic unit activity and behavior as observed with LSD. In addition, a low dose of psilocin (25 μg/kg, i.p.) produced no significant decrease in serotonergic unit activity in any of the cells tested, however, it did produce significant behavioral effects. Mescaline (5 mg/kg, i.p.) produced no overall significant change in unit activity (the discharge of three cells increased, three decreased, and two showed no change), but did produce large behavioral effects. Similarly, a low dose of DOM (50 μg/kg, i.p.) did not significantly affect any of the serotonergic units tested, but did have a significant behavioral effect. The highest dose of DOM (1 mg/kg), produced only increases in serotonergic unit activity, but nonetheless elicited significant behavioral changes. Furthermore, cells in the ventral portion of the dorsal raphe nucleus did not appear to be preferentially sensitive to either mescaline or DOM. Finally, although not extensively examined, the authors observed similar results, with various hallucinogens, in experiments on serotonergic neurons in nucleus centralis superior (Rasmussen, Heym, and Jacobs, unpublished observations).

Also examined were the effects of LSD upon unit activity of neurons in nucleus raphe pallidus, the most caudal group of serotonergic neurons in the cat brainstem. Somewhat surprisingly, the majority of neurons examined were almost completely unresponsive to doses of LSD (50 μg/kg, i.p.) and 5-MeODMT (50 μg/kg, i.m.) that produced potent behavioral effects (Heym, Steinfels, and Jacobs, submitted for publication).

The authors most recent study in this series provided perhaps the most damaging evidence to the presynaptic serotonergic hypothesis of hallucinogenic drug action, and began to focus their attention on the postsynaptic actions of these drugs. When cats were administered mianserin (0.1-1.0 mg/kg, i.p.), a serotonin postsynaptic antagonist, 30 minutes prior to LSD (50 μg/kg) or DOM (250 μg/kg), it blocked their behavioral effects in a dose-dependent manner. This did not appear to be due to nonspecific effects, since the drug produced no decrease in spontaneous activity and the animals did not appear to be sedated or cataleptic. Furthermore, mianserin exerted no blocking action on the behavioral effects of the dopamine agonist apomorphine. When animals were pretreated with mianserin (1 mg/kg, i.p.) and then administered LSD (50 μg/kg, i.p.) 30 minutes later, an almost complete blockade of the behavioral effects of LSD was observed, but no alteration of the 40-60 percent depression of serotonergic unit activity that LSD typically produces in neurons in nucleus raphe dorsalis and centralis superior (Heym, Rasmussen, and Jacobs, unpublished observations).

There are a number of other reasons for emphasizing the behavioral importance of the direct serotonergic postsynaptic effects of hallucinogenic drugs. However, space limitations will allow only a brief description of each of them.

1. Administration of a number of different hallucinogens produces behavioral effects indicative of a direct serotonergic agonist action at postsynaptic receptor sites. This is the elicitation of the so-called "serotonin syndrome" (Jacobs 1976). Evidence that this is a direct action is provided by studies which show that the effect is not blocked by prior serotonin depletion. Repeated administration of LSD diminishes its behavioral potency (tolerance) (Trulson et al. 1976). This is unaccompanied by a change in sensitivity of serotonergic neurons to LSD, but is accompanied by a decrease in the number of available serotonergic postsynaptic receptor binding sites (Trulson & Jacobs 1979c).

2. Studies in a variety of different species, including humans, demonstrated that prior depletion of serotonin enhances the behavioral effects of hallucinogenic drugs. In many of these cases there is direct evidence for the presence of serotonergic postsynaptic supersensitivity at the time the hallucinogens are administered.

3. In a variety of different paradigms, including drug discrimination, operant responding, and spontaneous behavior, the behavioral effects, in rat, of a number of hallucinogens can be effectively blocked by several different serotonin antagonist drugs.

4. Chronic administration of a monoamine oxidase inhibitor (MAOI) for 1 or 2 weeks can totally block the behavioral effects of LSD and other hallucinogens in rat, cat, and humans. This blocking action may persist for as long as 2 weeks

following withdrawal from the MAOI. Neurochemical evidence strongly indicates that this decreased response to hallucinogenic drugs is mediated by a decrease in the availability of postsynaptic binding sites for serotonin.

5. Binding of [^{3}H]-LSD, whether examined autoradiographically or using receptor specific binding assays, is unchanged by destruction of serotonergic neurons. Since much of this binding can be displaced with serotonin, it indicates that it is associated with serotonin receptors but, apparently, not those localized on various aspects of the presynaptic neuron.

In summary, it is well-known that hallucinogens, such as LSD, psilocin, mescaline, DMT and DOM, produce similar effects in humans and also display cross-tolerance of action. The most parsimonious explanation for these similarities is that these drugs share, at least to some extent, a common biological action. Evidence from a variety of disciplines, some of which was reviewed here, indicates that this common action is exerted upon the brain serotonin system. (Although various hallucinogens may interact with neurotransmitter systems other than serotonin, they do not do so universally.) It may be useful at this point to review what is known regarding the synaptic interactions between the hallucinogens and serotonin. Hallucinogens produce: 1) depression of the activity of serotonergic neurons (the so-called presynaptic action); 2) a modest inhibitory action at serotonin postsynaptic receptor sites in the forebrain, especially subcortically; 3) a strong antagonist action to serotonin's excitatory effects on its postsynaptic target sites in a variety of brain areas, especially in cerebral cortex and brainstem; and 4) a potentiation (or facilitation) of the facilitatory effect exerted by serotonin on excitatory inputs to its target sites in the brainstem and spinal cord. Thus, the interactions of the hallucinogens with the brain serotonin system are complex, with mixed agonist, antagonist, and modulatory effects. As argued above, however, the critical effect is probably exerted directly upon cells postsynaptic to brain serotonin-containing neurons.

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Interaction of Monoamine Blocking Agents with Behavioral Effects of N,N-Dimethyltryptamine

David M. Stoff,[1,3] Dilip V. Jeste, M.D.,[1] Egidio A. Moja, M.D.,[2] Ken A. Stauderman,[1] and Richard J. Wyatt, M.D.[1]

Among the methylated hallucinogenic indoleamines, N,N-dimethyltryptamine (DMT) has been the most extensively studied concerning its possible role in schizophrenia (Gillin et al. 1976, 1978). Since the 5-hydroxytryptamine (5-HT) deficiency hypothesis for LSD was first proposed in the early 1950s, an impressive body of neurochemical and electrophysiological evidence has accumulated suggesting that DMT (and other indole hallucinogens) acts via interference of central 5-HT neurotransmission (Jacobs & Trulson 1981). In addition to possessing a serotonergic component, DMT may exert some of its effects by acting on other interrelated neurotransmitter systems. While there are a large number of studies demonstrating an interaction between drugs affecting the major monoamines (serotonin, dopamine, norepinephrine) in brain and some of the behavioral effects of other hallucinogens (Wyatt et al. 1976), similar data for DMT are sparse and conflicting. The human data are consistent with a 5-HT deficiency hypothesis since the monoamine oxidase inhibitor (MAOI), iproniazid, attenuated the psychological effects of DMT (Sai-Halasz 1963) while the serotonin receptor antagonists (2-bromo-LSD, methysergide) potentiated its effects (Sai-Halasz 1962). However, different results have been reported in animals where MAOIs potentiate some autonomic and behavioral effects caused by DMT (Moore et al. 1975; Vasko et al. 1974) while DMT-induced behavioral effects are antagonized, potentiated, or unaffected by different 5-HT receptor blockers (Corne & Pickering 1967; Jenner et al. 1980; Kovacic et al. 1978; Smythies et al. 1972; Winter 1972). Although neuroleptics block some behavioral effects of DMT (Jenner et al. 1980; Quock et al. 1979; Shah & Hedder 1978), similar blockade occurs among structurally unrelated hallucinogens and even these effects can be attributed to a behaviorally depressant action of the neuroleptic itself.

The authors previously reported DMT-induced disruption of rat shuttlebox avoidance (Stoff et al. 1977), an effect that occurs under conditions where the 5-HT behavioral syndrome was not observed. Here, they present a detailed series of dose response studies showing that various monoamine blocking agents (dopaminergic: chlorpromazine, clozapine, haloperidol, pimozide, thioridazine, noradrenergic: phenoxybenzamine, propranolol; serotonergic: cinanserin, cyproheptadine, methiothepin, methysergide) were unable to influence the DMT effect, at doses which by themselves did not alter avoidance behavior; as expected, pargyline potentiated DMT (*see* Table). Furthermore, DMT-induced disruption was uninfluenced by chronic neuroleptic treatment and pretreatments with 1) 1-methyl-1, 2, 5, 6-tetrahydropyridine-3-(N-, N-diethylcarboxamide) hypothesized to act at the site of action for DMT (Smythies et al. 1972); 2) BC-105, which blocks some behavioral effects of the close chemical relative, 5-methoxy-DMT (Winter 1978); or 3) alpha-methyl-para-tyrosine (AMPT). Some of the antagonists employed have more than one pharmacological action and little, if anything, is known about the ability of these compounds to interact with the site of action of DMT.

The authors' results may be consistent with the action of DMT through systems besides the major monoamines. Other data suggest the involvement of tryptamine receptors in the action of LSD and similar compounds (Martin et al. 1978) and tryptamine, the proposed biosynthetic precursor of DMT, causes similar effects to DMT in the same animal model (Vogel & Cohen 1977). More recently, an involvement of the opioids has been suggested since DMT-induced bar press disruption was antagonized by morphine and methadone and potentiated by naloxone (Ruffing & Domino 1981; Ruffing et al. 1979). The role of these and other putative neurotransmitter and peptide systems in the action of DMT deserves further attention.

[1]Adult Psychiatry Branch, National Institute of Mental Health, St. Elizabeths Hospital, Washington, DC 20032.
[2]Institute of Neurology and Psychiatry, University of Cagliari, Cagliari, Italy.
[3]Current Address: Department of Psychiatry, University of Chicago, Chicago, IL 60637.

Table

Effects of Monoamine Blocking Agents on DMT-Disruption

Pretreatment	Dose (mg/kg)	Conditioned Avoidance Responses (mean ± SEM)		
		Pretreat Time (mins)	Saline	DMT 4 mg/kg
Saline	–	30	89.3 ± .5	65.5 ± 2
AMPT	100	3 hrs	88.3 ± 1.2	58.4 ± 6.9
BC-105	12	60	90 ± 3	67 ± 10
Chlorpromazine	2.5	30	85 ± 2.1	58 ± 6.2
Cinanserin	35	60	91 ± 7	65.6 ± 12.4
Clozapine	2.5	30	81.6 ± 4.5	69.7 ± 4.4
Clozapine, 15 times	2.5	30	85.2 ± 1.4	61 ± 3.8
Cyproheptadine	20	15	86.2 ± 5.1	61 ± 5.6
Haloperidol	.05	30	87.8 ± 4.4	69.4 ± 9.8
Haloperidol, 14 times	.10	30	88.9 ± .7	65 ± 7.1
Methiothepin	.07	30	82.5 ± 5.1	61 ± 4.1
Methysergide	40	30	87.8 ± 4.5	65 ± 9
Pargyline	75	24 hrs	87.6 ± 1.8	46.5 ± 4.1*
Phenoxybenzamine	1.25	60	78 ± 4.9	55.8 ± 12.3
Pimozide	.20	60	83.6 ± 2.6	67.8 ± 7.1
Pimozide, 14 times	.20	60	87.4 ± 2.1	67 ± 6.2
Propanolol	20	15	94.2 ± 1.7	65 ± 2.6
Thioridazine	3.75	30	83.3 ± 4.1	64 ± 4.4
Thioridazine, 14 times	7.5	30	86.2 ± 2.1	63 ± 2.1
THPC	20	30	88.4 ± 7.4	67.4 ± 13.4

Values are expressed as the number of avoidance responses over a 100-trial session; drug pretreatments were tested after criteria of a high and stable avoidance rate was achieved (see Stoff et al. 1977).

*$p < .05$; matched t for DMT vs. saline, independent t for DMT vs. drug pretreatment.

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Evidence for Opioids as Partial Antagonists for Indole Hallucinogens

Edward F. Domino, M.D.,[1, 2] and Diane M. Ruffing,[2]

Various observations have supported the hypothesis that endogenous opioid peptides are involved in psychoses either therapeutically or pathogenically (Rimón et al. 1980; Pickar et al. 1981). Prior to the advent of neuroleptics, opioids such as morphine were used historically to treat mental disease. Hence, the role of opioids in psychoses is obscure and complex. It was decided to use an animal model of drug-induced psychotic behavior to investigate this interaction further (Ruffing et al. 1979; Ruffing & Domino 1981). Several opioid agonists, antagonists, and synthetic enkephalin analogues were studied on N,N-dimethyltryptamine (DMT) and lysergic acid diethylamide (LSD-25) induced disruption of food-rewarded FR_4 bar-pressing behavior in the rat. The striking interactions observed are reported herein.

Method

Adult male Holtzman rats were maintained at 70 percent of their expected free-feeding weight. Stable food-rewarded fixed ratio 4 (FR_4) bar pressing behavior was established, followed by daily 60-minute bar pressing sessions for a minimum of days prior to injections. Animals were then randomly assigned to groups ($N = 5$-12), scheduling each rat to serve as its own control to compare hallucinogen-induced effects with and without assigned pretreatment drugs. Control groups were pretreated with 0.9 percent NaCl intraperitoneally (i.p.) prior to DMT (3.2-10.0 mg/kg) and LSD (0.1 mg/kg) injections. A minimum 7-day drug-free interval was observed between scheduled injections. Predetermined behaviorally noneffective pretreatment drug doses given 10-20 minutes prior to DMT or LSD were as follows: morphine sulfate and methadone hydrochloride (0.32-3.2 mg/kg), (+)-MR 2267 (5.6-10.0 mg/kg), (−)-MR 2266 (3.2 mg/kg), (+)-naloxone hydrochloride (3.2 mg/kg), (−)-naloxone hydrochloride (1.0-3.2 mg/kg), naltrexone (1.16-3.7 mg/kg), (+)- and (−)-WIN 44,441-2/3 enantiomers (1.47-3.52 mg/kg), Lilly 127623 (0.0032-0.32 mg/kg), and FK 33-824(0.0001-0.01 mg/kg). All drug dosages refer to free base and were administered i.p. Two-tailed Student's *t*-test paired comparison determinations, calculated according to Snedecor (1956), were used to analyze pretreatment and/or hallucinogen drug effect interactions (i.e., antagonism, potentiation, or no effect). Due to the limited quantity of (+)-naloxone HCl and (−)-MR 2266, incomplete dose-effect relations are reported.

[1]Department of Pharmacology, University of Michigan, Ann Arbor, MI 48109.
[2]Lafayette Clinic, Detroit, MI 48207.

Results

DMT (3.2-10.0 mg/kg) and LSD (0.1 mg/kg) induced a reproducible disruption of food-rewarded bar pressing. Characteristic DMT and LSD-induced gross behavioral effects (evident within 2-5 minutes following i.p. injections) consisted of: lying quietly with the eyes open in an excessively flattened position for prolonged intervals, periodic Straub tail, muscular twitching and/or body movements, circling in a flattened position or reverse crawling, splayed and/or extension of the hind limbs, periodic stereotypic repetitious body movements, sustained periods of arching, and disinterest in food and/or bar pressing. The DMT and LSD-induced gross behavioral effects described above or with pretreatment drugs were consistent in all groups tested excepting morphine, methadone, and (−)-MR 2266 pretreated groups. In the morphine pretreated animals fewer and less intense gross behavioral effects were observed with periodic interest in food and/or bar pressing. Paradoxically, intensified gross behavioral effects were observed in the methadone and (−)-MR 2266 pretreated groups (i.e., increased and excessive flattening with frequent sustained repetitious head/body movements and markedly increased Straub tail). At the cessation of drug effects the rats would appear normal and abruptly start and continue bar pressing at pre-injection response rates.

The opioid agonist pretreatment groups (Figure 1) showed selective biphasic effects, i.e., morphine (0.32-1.0 mg/kg) and methadone (0.32 mg/kg) antagonized the effects of DMT and LSD-induced bar pressing disruption, whereas larger doses of morphine (3.2 mg/kg) and methadone

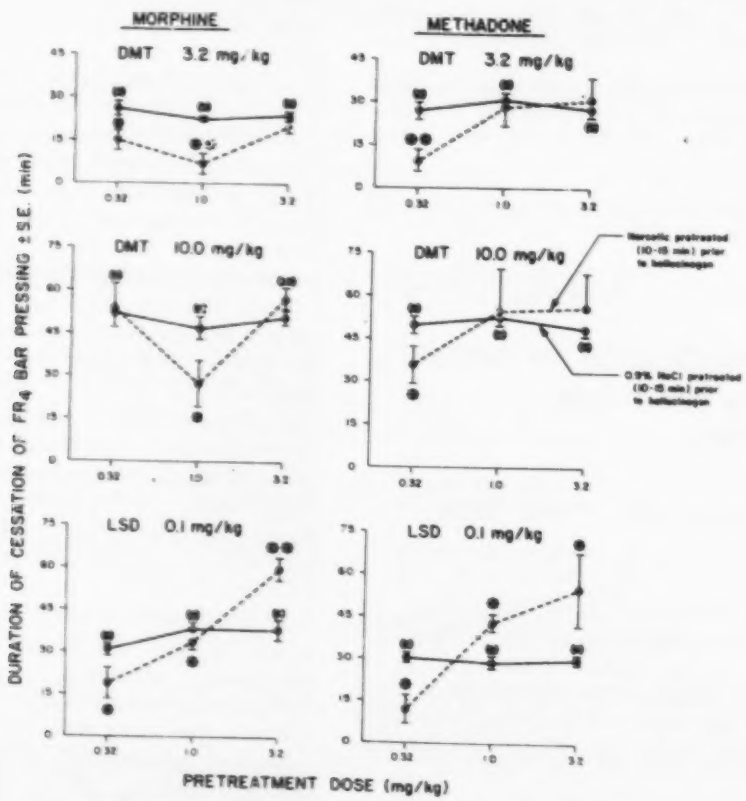

FIGURE 1. Effects of morphine and methadone pretreatment on DMT and LSD-induced disruption of FR_4 bar pressing behavior in the rat.

(1.0-3.2 mg/kg) selectively potentiated only LSD-induced effects with no differences noted in the DMT groups. The data indicate morphine as the more effective antagonist for DMT (3.2 mg/kg) and LSD-induced activity.

Conversely, the opioid antagonists, naloxone and naltrexone in pretreatment doses of 1.0-3.2 and 1.16-3.7 mg/kg, respectively, potentiated the behavioral DMT and LSD-induced effects as shown in Figure 2. Potentiation of DMT-induced effects was attributed to a stereospecific opioid antagonist effect of (−)-naloxone in that the (+)-naloxone enantiomer failed to interact or potentiate DMT (Ruffing & Domino 1981).

Pretreatment with stereo-isomers of two selected synthetic opioid antagonists, (+)-WIN 44,441-2, (−)-WIN 44,441-3, (+)-MR 2267, and (−)-MR 2266, unexpectedly demonstrated no interaction with DMT (3.2 mg/kg) induced disruption of FR_4 behavior, whereas both (+)- and (−)-WIN 44,441 enantiomers selectively potentiated the behavioral induced LSD effects, while only the (−)-MR 2266 stereo-isomer selectively antagonized behaviorally induced LSD effects (Figure 3).

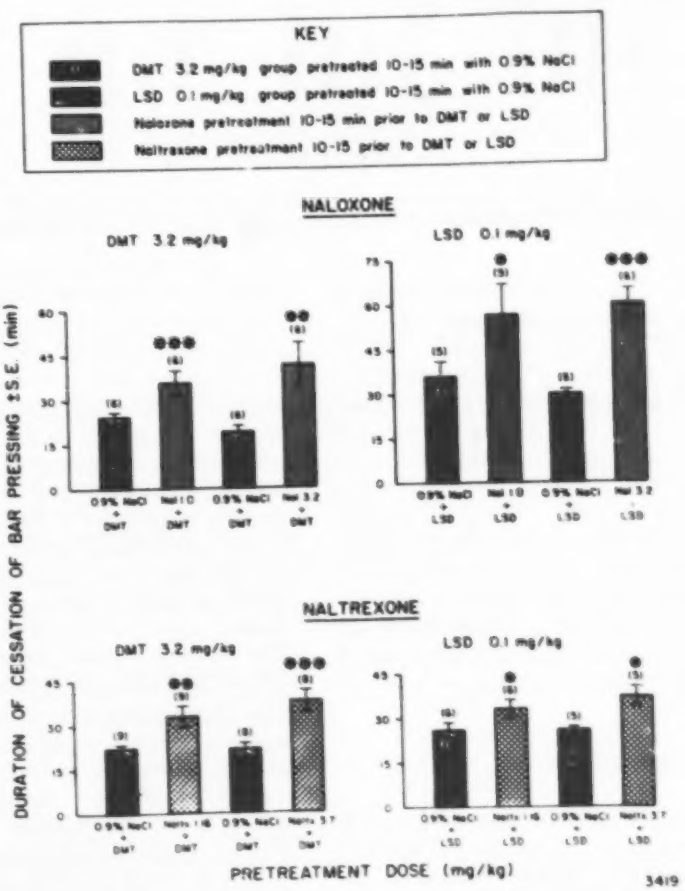
KEY
DMT 3.2 mg/kg group pretreated 10-15 min with 0.9% NaCl
LSD 0.1 mg/kg group pretreated 10-15 min with 0.9% NaCl
Naloxone pretreatment 10-15 min prior to DMT or LSD
Naltrexone pretreatment 10-15 prior to DMT or LSD
NALOXONE
DMT 3.2 mg/kg
LSD 0.1 mg/kg
NALTREXONE
DMT 3.2 mg/kg
LSD 0.1 mg/kg
DURATION OF CESSATION OF BAR PRESSING ±S.E. (min)
PRETREATMENT DOSE (mg/kg)
3419

FIGURE 2. Potentiation of DMT and LSD-induced disruption of FR_4 bar pressing behavior in rats pretreated with naloxone and naltrexone.

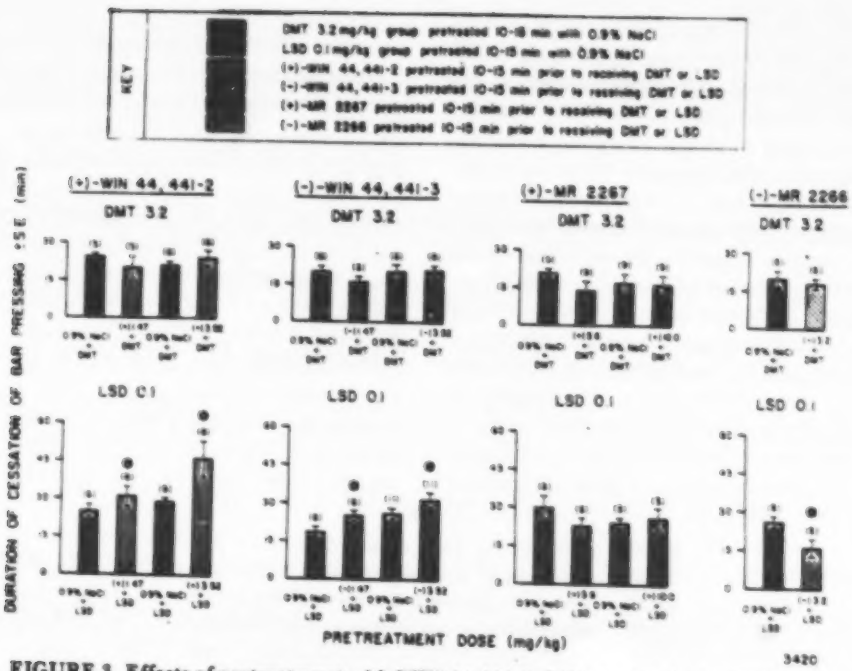

FIGURE 3. Effects of pretreatment with WIN 44,441-2, WIN 44,441-3, MR 2266, and MR 2267 on DMT and LSD-induced disruption of FR$_5$ bar pressing behavior in the rat.

As shown in the Table, the peptide synthetic enkephalinanalog pretreatment doses of Lilly 127623 (0.01-0.32 mg/kg) and FK 33-824 (0.001-0.01 mg/kg) significantly antagonized the effects of DMT (3.2 mg/kg), while pretreatment doses of Lilly 127623 (0.10-0.32 mg/kg) and FK 33-824 (0.00032-0.01 mg/kg) significantly antagonized the effects of DMT (3.2 mg/kg), while pretreatment doses of Lilly 127623 (0.10-0.32 mg/kg) and FK 33-824 (0.00032-0.01 mg/kg significantly antagonized LSD-induced effects. Additionally, Lilly 127623 (0.032 mg/kg) pretreatment also significantly antagonized the behaviorally induced disruptive bar pressing effects of DMT 10.0 mg/kg.

Discussion

The results of the present study extend previous observations that naloxone potentiated DMT and LSD-induced disruption of food-rewarded bar pressing in the rat (Ruffing et al. 1979). It is generally known that the biologically active narcotic antagonist is the (−)-naloxone isomer. Thus, it is of special interest that (+)-naloxone was inactive in potentiating the effects of DMT, confirming stereospecificity.

There is evidence that DMT and LSD, while sharing similar hallucinogenic effects, also show differences in the extent of dopaminergic and serotonergic agonist effects. For example, LSD has been shown to produce potent dopaminergic activity not produced by DMT (Nichols 1981). It is also abundantly clear that there are multiple neurotransmitter and opioid receptors, so that many of these agents differ in their molecular mechanism of action (Snyder & Goodman 1980). The present study indicates that the various opioid agonists and antagonists have very complex interactions with DMT and LSD. Although no simple theory explains all of the data obtained in this investigation, the present study indicates that there are very important interactions between these hallucinogens and opioids in the rat. The dramatic antagonistic effects of the opioid peptides, Lilly 127623 and FK 33-824, are especially prominent and deserve additional investigation with various behavioral paradigms in different species of animals including man.

Table

Mean Duration of DMT and LSD-Induced Disruption of Food-Rewarded FR_4 Bar Pressing in Control 0.9% NaCl Pretreated and Corresponding Lilly 127623 or FK 33-824 Pretreated Rats

Pretreatment Drug/Dose mg/kg (i.p.)	Mean duration of FR_4 bar pressing disruption (± S.E.) DMT 3.2 mg/kg (i.p.) (N)	Control 0.9% NaCl Pretreated	Drug Pretreated	p[a]	LSD 0.1 mg/kg (i.p.) (N)	Control 0.9% NaCl Pretreated	Drug Pretreated	p[a]
Lilly 127623 (0.0032)	(6)	26 ± 2	27 ± 3	N.S.	—	—	—	—
Lilly 127623 (0.01)	(10)	27 ± 2	12 ± 3	***	—	—	—	—
Lilly 127623 (0.032)	(10)	28 ± 2	10 ± 4	***	(6)	31 ± 2	27 ± 3	N.S.
Lilly 127623 (0.10)	(12)	26 ± 1	14 ± 3	*	(8)	29 ± 1	10 ± 3	***
Lilly 127623(0.32)	(10)	27 ± 3	14 ± 4	*	(8)	28 ± 3	18 ± 2	*
FK 33-824 (0.0001)	-	-	-	-	(6)	30 ± 1	32 ± 3	N.S.
FK 33-824 (0.00032)	(6)	28 ± 2	25 ± 1	N.S.	(9)	29 ± 1	11 ± 4	***
FK 33-824 (0.001)	(8)	26 ± 2	7 ± 3	***	(8)	31 ± 1	13 ± 3	***
FK 33-824 (0.0032)	(6)	25 ± 3	14 ± 3	*	(8)	27 ± 3	10 ± 4	*
FK 33-824 (0.01)	(6)	30 ± 4	24 ± 5	*	(6)	29 ± 2	19 ± 2	**

Pretreatment Drug/Dose mg/kg (i.p.)	DMT 10.0 mg/kg (i.p.) (N)	Control 0.9% NaCl Pretreated	Drug Pretreated	p[a]
Lilly 127623 (0.032)	(6)	51 ± 3	21 ± 7	**

All pretreatment injections were given 15-20 min prior to DMT or LSD.
p, values represent paired comparison t tests.
$^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$; N.S. - not significant

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In Vitro Models to Examine Regulation of Transmitter Content and Adenylatecyclase Coupled Receptors in Neurons[1]

David C. U'Prichard, Ph.D.,[2,3] Karen M. Braas, B.S.,[2] and Deborah J. Kahn, B.S.[2]

Major psychoactive drug classes such as antidepressants and neuroleptics are now believed to exert their therapeutic effects by inducing long-term changes in receptor function at brain monoamine synapses. Chronic antidepressant treatment of rats, for example, causes a reduction in brain β_1-adrenergic receptor number and a down-regulation of both the proximal biochemical response, stimulation of adenylate cyclase activity (Wolfe et al. 1978; Moyer et al. 1981), and electrophysiological responses of neurons associated with β-receptor activation (Schultz et al. 1981). However, with other brain monoamine receptors there are apparent discrepancies between the effects of antidepressant treatment on receptor number obtained from binding studies, and receptor-mediated responses. Thus antidepressant treatment down-regulates the number of brain serotonin-2 (S2) receptors measured with ^{3}H-spiroperidol (Peroutka & Snyder 1980a, 1980b), but appears to cause serotonin receptor supersensitivity in electrophysiological experiments (de Montigny & Aghajanian 1978).

Similarly, although antidepressant treatment causes a functional subsensitivity of brain and peripheral α_2-adrenergic receptors (Crews & Smith 1980; McMillen et al. 1980), studies examining changes in binding of the agonist ligands ^{3}H-clonidine (CLO) and ^{3}H-*p*-aminoclonidine (PAC) to brain α_2-receptors have produced conflicting results, with antidepressant treatment reducing the B_{max} of ^{3}H-CLO in rat brain regions other than cortex (Smith et al. 1981) and clinically in human platelets (Garcia-Sevilla et al. 1981), while other laboratories, including the present investigators, observed that in rats, abbreviated (3 days) treatment with desmethylimipramine or iprindole increased the B_{max} of ^{3}H-PAC or ^{3}H-CLO (Reisine et al. 1980; Johnson et al. 1980). The investigators have also found that chronic immobilization stress down- regulates β-receptors in different rat brain regions, but causes an increase in the B_{max} of ^{3}H-CLO in cortex, and a decrease in the B_{max} of ^{3}H-CLO in other brain areas (U'Prichard & Kvetnansky 1980).

The investigators attempted to reconcile these differences between drug-induced binding and functional changes by investigating the mechanisms of monoamine receptor down-regulation as a result of chronic agonist exposure in cloned neural cells in culture. In particular, they were interested in comparing the mechanisms of down-regulation of receptors that stimulate adenylate cyclase (positively coupled), and of receptors that inhibit adenylate cyclase (negatively coupled). Among the former class are β-adrenergic, dopamine D1, and serotonin S1 receptors, while the latter class includes α_2-adrenergic and dopamine D2 receptors. S2 receptors show GTP-sensitivity (Hamon et al. 1980), and may turn out also to be negatively coupled to adenylate cyclase. Receptors of either class occur in two or more affinity states, mainly differentiated with respect to agonists, referred to as H (high) and L (low). Guanine nucleotides shift equilibrium between H and L states in favor of L, and so promote coupling of either type of receptor with adenylate cyclase (Hoffman & Lefkowitz 1980). An important corollary to this model is that whereas the B_{max} of an antagonist radioligand is likely to be a true indicator of total receptor density, the apparent B_{max} of an agonist ligand, measured over restricted ligand concentrations, will be more an index of the number of H states of the receptor rather than of total receptor density, and changes in the B_{max} of agonist ligands may indicate a shift in the equilibrium between H and L states, and thus altered receptor-effector coupling, rather than a change in receptor number.

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[2]Department of Pharmacology, Northwestern University Medical School, Chicago, IL 60611.

[3]Department of Neurobiology and Physiology, Northwestern University College of Arts and Sciences, Evanston, IL 60201.

Address Correspondence to: Dr. David C. U'Prichard, Department of Pharmacology, Northwestern University Medical School, 303 E. Chicago Ave. Chicago, IL 60611.

A number of laboratories have examined the molecular characteristics of β-receptor down-regulation in cultured neural cells. Su et al. (1980) have analyzed the consequences of exposure of 1321N1 human astrocytoma cells to the β-agonist isoproterenol. Through combined measurements of binding and cyclase response, they determined that 1321N1 β-receptors are down-regulated in two phases, the first being an uncoupling of receptors from adenylate cyclase, with a shift from H to L forms of the receptors, but no change in total receptor population, followed by a second long-term phase of loss of receptor number.

The investigators have examined regulation of the negatively coupled α_2-receptor on cultured neuroblastoma x glioma NG108-15 hybrid cells. These cells are cholinergic in nature, synthesize and release acetylcholine, and contain negatively coupled α_2-adrenergic, opiate and muscarinic cholinergic receptors. The investigators found immunocytochemical staining at the LM and EM level with anti-met^5-enkephalin and anti-leu^5-enkephalin antibodies in undifferentiated cells grown in serum-containing and serum-free defined medium. At the EM level, staining was localized to synaptic vesicles. No staining with β-endorphin or β-LPH antibodies was observed. These cells therefore synthesize enkephalin peptides as well as acetylcholine. In undifferentiated cultures, only 25-30 percent of the cells stained for enkephalins, and staining was localized to rounded or neurite-like cells either singly or in small clusters. When the cells in either medium were induced to differentiate with 1.0 mM dibutyryl cyclic AMP (dBcAMP) in the medium for up to 5 days, there was a progressive increase in the percent of the volume fraction of cells staining, up to 60-70 percent (Figure 1). Staining in differentiated cells was intense throughout the elongated processes which developed and, at the EM level, cells had an increased number of vesicles staining for enkephalins. Thus differentiation of these (and other) neural cells in culture caused greatly increased synthesis of opioid peptides (Braas et al. 1981).

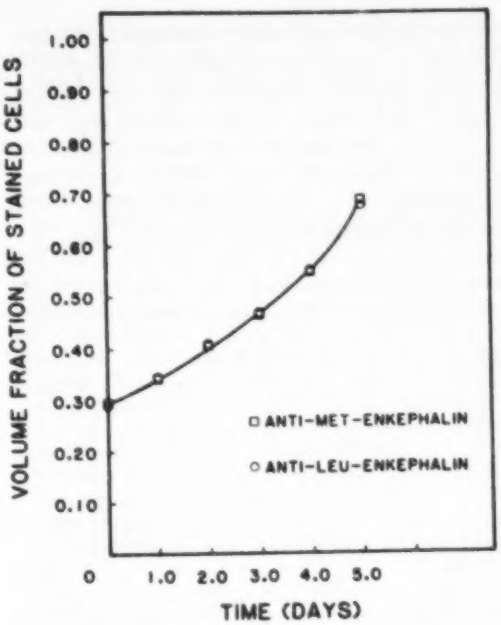

FIGURE 1. Increase in volume fraction of NG 108-15 cells in culture staining for met-enkephalin and leu-enkephalin, as a function of time of incubation of cells with 1.0 mM dBcAMP.

Alpha$_2$-receptors on undifferentiated NG108-15 cells in either medium were labeled with the full agonist ^{3}H-epinephrine (EPI), the partial agonist ^{3}H-PAC, and the antagonists ^{3}H-yohimbine (YOH) and ^{3}H-rauwolscine (RAUW). The NG108-15 α_2-receptor was shown to occur in two states with ^{3}H-EPI and ^{3}H-PAC selectively labeling H, and ^{3}H-YOH and ^{3}H-RAUW labeling both H and L. The total density was 30,000-40,000 receptors per cell. Guanine nucleotides and divalent cations modulated the equilibrium between H and L states as observed for other cyclase-linked receptors (Kahn et al. 1982). To examine regulation, cells were exposed to (−)-epinephrine at 37°C for 0.1-16.0 hours, and binding of various ligands, and the response of inhibition of basal adenylate cyclase was measured in thoroughly washed membranes. The time course of binding and response changes is shown in Figure 2. Like β-receptors, regulation of NG108-15 α_2-receptors by 10 μM (−)-epinephrine appeared to be biphasic. At short exposure times (less than 60 min), there was a shift from L to H states of the receptor, as indicated by an increase in the B_{max} of ^{3}H-EPI and ^{3}H-PAC, with no change in total receptor number (B_{max} of ^{3}H-RAUW), while at the same time there was no change in the maximum receptor-mediated response, but there was a 2-fold reduction in the potency of (−)-epinephrine in inhibiting adenylate cyclase. Therefore this first

phase of regulation represents uncoupling of the receptor with a concomitant shift to H (desensitized?) states. At longer exposure times there was a progressive reduction in receptor number measured with any ligand, accompanied by no change in maximum response (Figure 2), but a reduced potency of (−)-epinephrine, suggesting the presence of a spare receptor reserve. Other experiments indicated that in this second phase of down-regulation, there was a selective loss of H states of the receptor (Kahn & U'Prichard 1981).

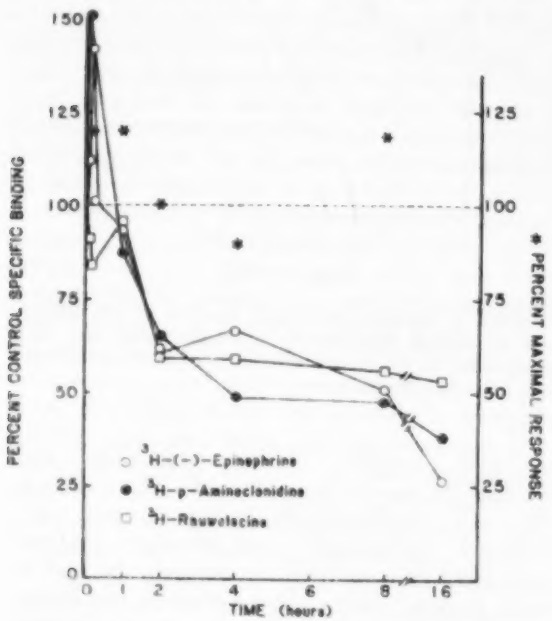

FIGURE 2. Changes in α_2-receptor binding (B_{max}) and adenylate cyclase response (inhibition by epinephrine) in washed membranes as a function of time of exposure of NG108-15 at 37° to 10μM (−)-epinephrine.

In other experiments, rats under mild restraint were continuously infused for 72 hours via the jugular vein with clonidine (0.001-1.0 mg/kg/hr). Infusion of clonidine had a bimodal effect on rat cortex ^{3}H-PAC sites, with lowest concentrations of clonidine increasing ^{3}H-PAC binding 50 percent above control, while higher doses decreased ^{3}H-PAC binding 60 percent below control values. However, rat cortex ^{3}H-RAUW binding (Perry & U'Prichard 1981) was not affected at any clonidine concentration (U'Prichard et al. 1981). This dose-dependent regulation of H states of the α_2-receptor with no change in total receptor population following a fixed time of agonist exposure may parallel the time-dependent bimodal regulation of agonist binding with a fixed concentration of agonist seen in NG108-15 cells.

The above results indicate that there is a phase of α_2-receptor down-regulation where one can observe an *increase* in agonist binding. It is clear that the relationship between changes in monoamine receptor binding and function due to increased agonist exposure, e.g., as a result of antidepressant treatment, can be quite complex, and apparently contradictory data can be obtained which are resolvable once the true significance of binding changes is understood. Regulation of neuronal serotonin receptors and responses can be analyzed in a parallel manner through the use of serotonin receptor-containing neuroblastoma hybrid NG108-15 and NCB-20 cells in culture.

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Mental Illness in Pregnancy and the Puerperium

Chair: Merton Sandler, M.D.
University of London
Queen Charlotte's Maternity Hospital
London, England

Model Utility in Postpartum Psychosis

James A. Hamilton, Ph.D., M.D.[1]

Over the past half-century many physicians have suspected that severe psychiatric illness which follows childbearing, or postpartum psychosis, is critically related to hormonal changes in the puerperium (Karnosh & Hope 1937; Bürgi 1953). The author noted that very little progress has been made toward translating the suspicions of hormonal involvement into therapeutic applications. Postpartum patients continue to be treated as if they have run-of-the-mill psychiatric diseases, often with unsatisfactory results.

Among the reasons cited for current failure to explore and exploit a likely hormonal component is the fact that the presenting psychiatric syndromes of postpartum patients vary widely and may change abruptly or slowly to other syndromes. Mixed syndromes are of frequent occurrence. Along with the instability of clinical syndromes is a complex and rapidly-changing hormonal situation. The complexity and changeability of the psychiatric and hormonal situations have worked against definitive analysis. Furthermore, the severity of illness, with grave suicidal hazards, has discouraged the pursuit of studies with traditional experimental controls.

The author suggested that the understanding and treatment of patients might profit by the use of models, an approach which has been useful in other complex scientific problems. Specifically, he suggested that known hormonal events be plotted in temporal sequence on a logarithmic scale. Psychiatric phenomena would be superimposed on this scale. In the interest of simplicity, the first model would be limited to a distribution of the first occurrence of symptoms in patients with two constellations of symptoms, those exhibiting agitation ranging to mania, and those whose illness begins with depression. When mixed cases are eliminated, there is reasonable agreement that the first symptoms of the agitated group usually develop from the 4th to the 12th day postpartum, while the first symptoms of the depressed patients usually begin from the 3rd to the 5th week (Karnosh & Hope 1937; Paffenbarger et al. 1961; Pauliekhoff 1964).

Figure 1 indicates thyroid changes in the puerperium. The only comprehensive data on this were reported in 1943 (Danowski). The standard of measurement was protein-bound iodine (PBI), so there is no separation of thyroid fractions. With a pre-pregnancy mean of 5.40, the final mean, 280 days after childbearing, is 4.40. The standard deviation of the final measure is 0.90, so many values are far below the pre-pregnancy range. The author recalculated Danowski's data to eliminate nursing mothers and cases of amenorrhoea and found a value of 4.46 at 280 days. With estrogen cycles back to normal it is difficult to ascribe this low level to anything else than a

[1]Suite 1515, 490 Post Street, San Francisco, CA 94102.

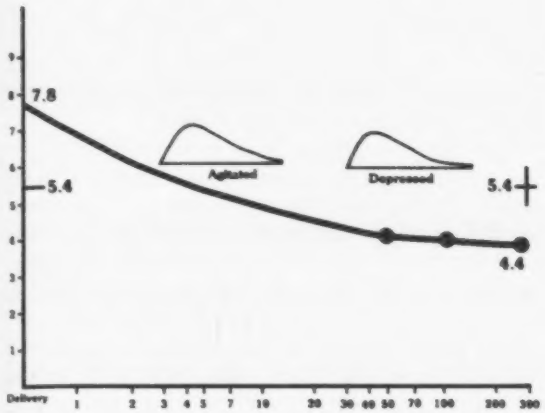

FIGURE 1. Late depression and mean PBI levels.

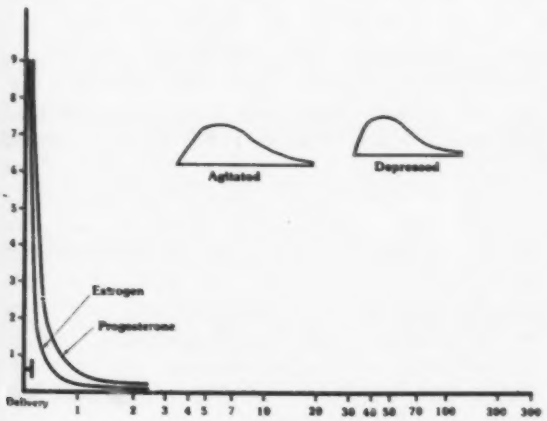

FIGURE 2. Estrogen and progesterone.

substantial, long-lasting drop in the output of thyroxine.

The author noted that postpartum symptoms which begin with depressive symptoms tend to occur as the PBI drop reaches the beginning of its low plateau. Two clinicians with large numbers of cases have reported independently that many cases of depression in the late puerperium respond favorably to thyroid administration, but this form of treatment is not widely accepted (Hamilton 1962; Baker 1967).

Figure 2 indicates the postpartum drop in fetoplacental hormones. The author noted that estrogen and progesterone are at very low levels within 24 hours after delivery, while symptoms of psychiatric illness almost never appear before the 3rd or 4th day. He pointed out that this fact makes it unlikely that deprivation of fetoplacental

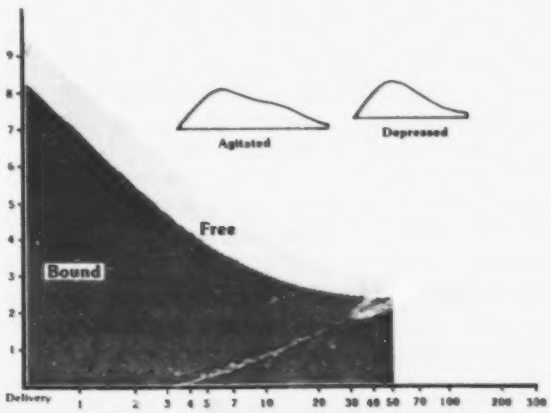

FIGURE 3. Adrenal corticoids: The trend.

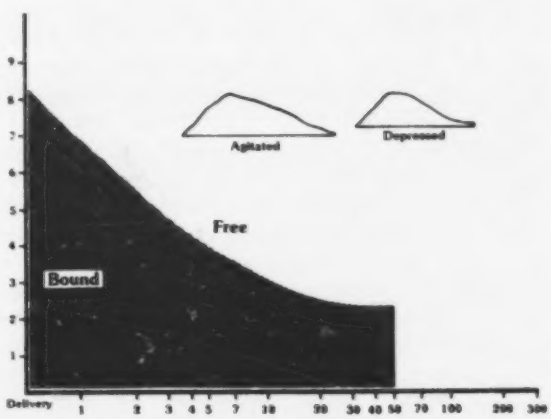

FIGURE 4. Variability of free cortisol: A possible cause of early symptoms.

hormones acts *directly* to produce psychiatric symptoms. Indirect causal effects are not ruled out, and indeed there is some indication that if the postpartum fall in estrogen is cushioned by parenteral estrogen at delivery and for a few days thereafter, high-risk patients may be protected from recurrence of postpartum illness (Hamilton 1977).

Figure 3 is a crude portrayal of the postpartum changes in adrenal corticoids (Tulchinsky 1980). During the latter part of pregnancy, total serum corticoids rise to a level which is three times that of the nonpregnant state. Most of the corticoids are bound to a specific protein, transcortin. About 90 percent of the principal corticoid, cortisol, is bound while 10 percent is free. As corticoids fall over a period of 2 to 3 weeks postpartum, the tendency is for free, physiologically active cortisol to decrease at about the same rate.

However, the author pointed out evidence from the work of Sachar and others indicates that the input of new free cortisol is pulsatile, so that the decrease in corticoids is probably more correctly represented in Figure 4 (Sachar 1973).

The maintenance of optimal levels of free cortisol is mainly achieved through a feedback sensing mechanism located in the hypothalamus. This mechanism generates a peptide releasing factor which is carried by the primary capillary plexus to the anterior pituitary, which in turn releases adrenocorticotropic hormone (ACTH) and thereby stimulates the production of cortisol (Jubiz 1979).

After childbirth the pituitary moves rapidly from hyperemia to ischemia, and its cells change from a phase of hyperactivity to a resting phase. This is reflected in the observation that the postpartum pituitary response is "sluggish" (Tulchinsky 1980).

Inspection of Figure 4 leads directly to a hypothesis with regard to early, agitated postpartum symptoms. During the first 10 days postpartum, total corticoids remain fairly high, but the principal active component, free cortisol, is variable. It may reach a low point, inciting a reaction by its sensor in the hypothalamus, but the response of the "sluggish" pituitary may be insufficient to stimulate the required amount of new free cortisol. The sensor continues to respond, perhaps more and more vigorously. Increased hypothalamic activity may spread to other hypothalamic functions, with sleep disturbance and heightened sympathetic activity, which is perceived as severe anxiety. This kind of disturbance, in the absence of a reasonable cause, could lead to the thinking disturbances which are observed in early postpartum cases.

The foregoing hypothesis is supported by experimental evidence which was reported 8 years ago by Steiner and his associates (1973). These workers treated alternate admissions of early postpartum psychosis with propranolol and chlorpromazine. Only five patients were included in each group, but admission data indicated excellent group comparability. The results with propranolol were strikingly and uniformly better than the results with chlorpromazine. This study, which may well be a landmark in the treatment of postpartum psychosis, has been virtually disregarded. The use of propranolol, a drug with many receptor sites in the hypothalamus, may be a specific medication for responses which can evolve rapidly into early postpartum psychosis.

To explore the model-generated hypothesis further, the author used small doses of propranolol with small doses of sedation to treat a case of known (iatrogenic) corticoid withdrawal which had been unresponsive to other treatment. Symptoms of episodic palpitation, severe anxiety and visceral distress, dyspnea, sleep disturbances and panic which had persisted for 3 months were relieved immediately. The symptoms were very similar to those found in early postpartum cases. The difference was in the response to symptoms. The patient was aware of the event which had precipitated her symptoms.

The case of known corticoid withdrawal is not submitted as a necessary equivalent to early postpartum cases. It is, rather, an instance in which a model-generated hypothesis can stimulate cautious clinical experimentation along lines relating to the area of the hypothesis.

In summary, models can be useful in the visualization of complex psychophysiological relationships, such as may exist in postpartum psychosis. Models, such as that presented, could be useful in relating experimental findings and clinical observations which, without a model, are likely to remain isolated, disconnected, unexplored and neglected. An outstanding and unacceptable fragmentation of this kind is found in the area of psychiatric illness which follows childbearing.

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Hormonal Modulation of Central Dopamine Receptor Sensitivity in the Postpartum Period

Umberto Scapagnini, M.D.,[1] Filippo Drago, M.D.,[1] Ferdinando Nicoletti, M.S.,[1] Francesco Patti, M.S.,[1] Mario Matera, M.D.,[1] and Pier L. Canonico, M.D.[1]

It has long been known that neurological or psychiatric disturbances may occur in women in the course of physiological disendocrine states. Depression and/or anxiety, for instance, are frequent in the premenstrual syndrome (Reid & Yen 1981), while there is evidence that postmenopausal women have the highest incidence of tardive dyskinesia (Crane 1968). The postpartum period is associated with sharp hormonal modification, including changes in prolactin (PRL), 17-β-estradiol, or progesterone levels (Rolland et al. 1976).

In the present study, the authors focused attention on the central effects of PRL, estrogens (E), and progesterone (PG) in an attempt to establish whether changes in hormonal levels may be involved in the occurrence of neuropsychiatric disorders, including psychosis, in the postpartum period (Hatotani et al. 1980). As a first step, the authors investigated the effects of PRL, E, or PG on dopaminergic transmission which is apparently implicated in the pathophysiology of psychiatric or extrapyramidal syndromes. Toward this end, the effects of PRL on dopamine (DA)-dependent behaviors such as grooming or motor behavior were investigated in male rats. Animals displayed excessive grooming in conditions of chronic endogenous hyperprolactinemia induced by anterior pituitary transplantation under the kidney capsule (Table 1). This increase in grooming behavior is considered as a consequence of PRL-induced stimulation of nigro-striatal DAergic transmission since it is elicited by i.c.v. or intranigral PRL injection (Table 1). The grooming is apparently prevented by intrastriatal injection of haloperidol or 6-hydroxy-DA injection (Table 1).

[1]University of Catania, Catania, Italy.

Table 1

Influence of PRL on Grooming Behavior

Treatment	Grooming Score
Pituitary homograft	89.0 ± 5.0*
Smooth muscle graft	15.0 ± 2.0*
i.c.v. PRL + intrastriatal saline	72.8 ± 6.1**
i.c.v. PRL + intrastriatal haloperidol	24.2 ± 2.0**
i.c.v. PRL + intrastriatal 6-OHDA	44.9 ± 4.2†
i.c.v. saline + intrastriatal saline	26.2 ± 4.1
Intranigral saline	21.2 ± 2.2
Intranigral PRL	84.7 ± 5.0‡

Values are mean ± S.E.
*p = 0.01 (Student's t-test) in comparison with smooth muscle graft;
**p = 0.01 and
†p = 0.05 (Dunnett's test) in comparison with i.c.v. + intrastriatal saline-injected animals;
‡p = 0.01 (Student's t-test) in comparison with intranigral saline-injected animals.

As evidence for the hypothesis of a PRL interference with central DAergic function, graft-induced hyperprolactinemia significantly potentiates apomorphine or amphetamine-induced stereotypies (Table 2) and PRL increases striatal DA turnover *in vitro* (Perkins & Westfall 1978). However, the lack of *in vivo* biochemical evidence led the authors to investigate whether PRL may interfere with DA-dependent messages by influencing other neural system functionally linked to DAergic transmission. In this connection, it is remarkable that i.c.v. PRL injection results in a decrease in striatal acetylholine turnover (Wood et al. 1980). In view of the well-documented functional linkage between nigro-striatal DAergic and striato nigral GABAergic transmission (Bartholini et al. 1977), the authors have investigated the effects of hyperprolactinemia on the activity of the GABA-synthesizing enzyme glutamate decarboxylase (GAD, EC 4.1.1.15) in substantia nigra (SN). This parameter mainly reflects the synthesis of GABA at the levels of nigral nerve endings originating from corpus striatum (Fonnum et al. 1974). A significant increase of plasma PRL levels (Table 3) is observed under conditions of hyperprolactinemia resulting from anterior pituitary homograft or acute or chronic injection of sulpiride, a hyperprolactinemic neuroleptic that, at the dose used (2 mg/kg, i.p.), poorly crosses the blood-brain barrier (Benakis & Rey 1976). Involvement of PRL in the effects of sulpiride is also suggested by the evidence that no change in nigral GAD activity is observed in sulpiride-injected hypophysectomized animals (Table 3). Thus, it is tempting to speculate that PRL interferes with the extrapyramidal motor system by influencing, at least in part, strio-nigral GABAergic transmission.

Table 2

Effect of Endogenous Hyperprolactinemia on Apomorphine or Amphetamine-Induced Stereotypes

Treatment	Time (sec) Sham Op.	Graft
Saline, i.p.	18.2 ± 1.6	16.2 ± 1.5
Amphetamine (1mg/kg, i.p.)	30.3 ± 3.6	78.4 ± 4.6*
Saline, i.p.	20.4 ± 1.8	18.3 ± 2.0
Apomorphine:		
100 μg/kg, s.c.	41.7 ± 2.2	67.3 ± 4.8**
250 μg/kg, s.c.	83.7 ± 5.9	199.6 ± 8.4**

Values are mean ± S.E.
*p = 0.01 (Student's t-test) in comparison with sham-operated amphetamine-injected animals;
**p = 0.01 in comparison with sham-operated apomorphine-injected animals.

Table 3

Effects of PRL on Nigral GAD Activity

Treatment	Nigral GAD Activity ($\mu mol^{14}CO_2$/100mg prot./60 min)	PRL (ng/ml)
Smooth muscle graft	41.57 ± 2.20	22.3 ± 1.9
Anterior pituitary graft	55.28 ± 0.21*	64.6 ± 4.1*
Saline, i.p.	41.78 ± 4.10	19.9 ± 2.4
Acute sulpiride (2 mg/kg, i.p.)	59.06 ± 7.44**	73.4 ± 6.2**
Chronic sulpiride (2.5-5 mg/kg, i.p.)	59.97 ± 9.75**	65.6 ± 4.7**
Saline, i.p. + hypophysectomy	39.13 ± 6.52	3.2 ± 0.9
Acute sulpiride + hypophysectomy	42.58 ± 4.93	2.8 ± 1.1
Sesam oil	42.36 ± 5.41	21.2 ± 2.5
Estradiol benzoate (5 μg/rat)	32.69 ± 3.95†	53.8 ± 5.1†

Values are mean ± S.E.
*p = 0.01 (Student's t-test) in comparison with sham-operated;
**p = 0.01 (multiple variance analysis test) in comparison with saline-injected animals;
†p = 0.01 (Student's t-test) in comparison with sesame oil-injected animals.

Several studies were performed concerning the influence of E on nigro-striatal DAergic transmission. Specifically, in view of clinical and animal studies, E appear to decrease DAergic tonus. In this line, E have been shown to display a striking effect on L-DOPA or neuroleptic-induced dyskinesia (Bèdard et al. 1979). Moreover, E appeared to potentiate spiperone-induced catalepsy (Chiodo et al. 1979), decrease apomorphine-induced stereotypies (Euvrard et al. 1980), impair DA response on striatal cholinergic interneurons (Euvrard et al. 1979) and increase the number of DA receptors (Hruska et al. 1980). Since hypophysectomy completely prevents these effects (Euvrard et al. 1979; Hruska et al. 1980) it has been proposed that the anti-DAergic activity of estrogens might be mediated by PRL, the secretion of which is strongly stimulated by E (Labrie et al. 1978). However, as above reported, PRL presumably potentiates the DA-related behavioral parameters. We have also demonstrated (Table 3) that E treatment results in a decrease of nigral GAD activity in spite of the high PRL levels. Thus, it is conceivable that PRL does not mediate E central effects but rather displays an opposite effect in comparison with E, at least with respect to the striato-nigral GABAergic system.

In regard to PG, no data concerning a possible interference with the extrapyramidal motor system are available. However, in view of the evidence that pregnancy or oral contraceptive therapy are sometimes associated with chorea (Fernando 1966), it has been suggested that PG can increase DAergic transmission (Bèdard et al. 1979). In the present study we have investigated the effects of PG in patients affected by Parkinson's disease. A preliminary clinical evaluation carried out using semiquantitative scales and electromyography would indicate that PG, in association with L-DOPA + decarboxylase inhibitor (DI) improves the therapeutic efficacy of L-DOPA + DI significantly more than a placebo. This evidence would be consistent with the DAergic hypothesis of PG central effects, even though the mechanism of action of the sexual hormone remains unclear.

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Membrane Lipids in Neuropsychiatric Disorders

Co-Chair: David L. Garver, M.D.
Department of Psychiatry
University of Cincinnati
School of Medicine
Cincinnati, Ohio

and

John Rotrosen, M.D.
Psychiatry Service
VA Medical Center
New York, N.Y.

Membrane Abnormalities in Schizophrenia[1]

Robert Hitzemann, Ph.D.,[2] and David Garver, M.D.[2]

Introduction

Recent studies from this laboratory have described a lithium-responsive schizophrenia (Hirschowitz et al. 1980). This disorder is characterized by an acute and remitting illness and thus such patients meet the criteria both for "good prognosis schizophrenia" (McCabe et al. 1971) and Diagnostic and Statistical Manual-III (DSM-III) schizophreniform disorder. In addition, these patients, in contrast to non-lithium responders, show an excessive growth hormone response to apomorphine (Hirschowitz et al. 1982) and an elevated erythrocyte lithium ratio (Garver et al. 1982). The increase in lithium ratio appears to be related to a decrease in Na^+-Li^+ counterflow activity and in some patients to an increase in passive Li^+ leak.

It was hypothesized that the abnormalities in Li^+ transport may be a reflection of a more general abnormality in membrane composition. Indeed, preliminary studies (Hitzemann & Garver 1981) revealed that there was a significant decrease in phosphatidylcholine (PC) levels in the erythrocyte ghost membranes of high lithium ration—good prognosis patients. The magnitude of the decrease in PC is similar to that reported by Stevens (1972) for a general schizophrenic population and subsequently confirmed by Henn (1981).

These authors found an increase in phosphatidylserine (PS) to compensate for the decrease in PC. These data differ from the results in schizophreniform patients where ethalolamine plasmalogen (EP) or sphingomyelin (SP) levels were found to increase in the PC deficient membranes (Hitzemann & Garver 1982). Thus, there is some evidence that there may be differences between schizophrenic and schizophreniform patients as to the membrane lipid abnormalities. In order to examine this issue in greater detail, the authors studied the erythrocyte ghost lipid com-

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[2]Department of Psychiatry, University of Cincinnati School of Medicine, Cincinnati, OH 45267.

position of 23 DSM-III schizophrenics, 9 DSM-III schizophreniform patients, and 15 age- and sex-matched controls. The possibility was also examined that the membrane abnormalities in the lithium-responsive schizophreniform patients may impart some unique mechanisms of action to lithium. The first site examined was the phospholipid methylation system (Hirata & Axelrod 1980), since it seemed conceivable that lithium could stimulate methylation and reverse the decrement in membrane PC at critical sites for the regulation of membrane activity.

Method

The patient population used in this study has been described previously (Hirschowitz et al. 1980). All patients undergo a 2-week drug washout prior to sampling. Four of the schizophreniform patients had no prior history of drug use. Three of the control patients had common migraine and were under treatment, aspirin and/or propranalol, for this disorder. Ghost membranes were prepared from well-washed red cells as described by Dodge et al. (1965). The membranes were then analyzed for the content of the major phospholipid classes as described by Horrocks (1968). Phospholipid methylation was measured in *fresh* ghost membranes at pH = 8.0 essentially as described by Crews et al. (1980).

The methylated products were isolated by thin-layer chromotography (Crews et al. 1980). The amount of radioactivity found in phosphatidylethanolamine (PE) was taken to be the blank value and was subtracted from the counts in phosphatidylmonomethylethanolamine (PME), phosphatidyldimethylethanolamine (PDC), and PC. Statistical significance was determined by the Student's *t*-test for unpaired data.

Results and Discussion

The data in Table 1 show that there was a significant decrease from control levels in erythrocyte ghost PC for both the schizophrenic and schizophreniform groups. For most patients, this deficiency in PC was compensated by an increase in SP. Thus, the total amount of lipid-choline (PC + SP) was conserved. These data differ from previous results for schizophreniform patients (Hitzemann & Garver 1982) in which the decrement in PC was primarily compensated by an increase in EP. In this study, the increase in EP was observed in 2 of the 23 schizophrenic and 4 of the 9 schizophreniform patients, suggesting the greater incidence of the EP change in schizophreniform patients but not as great an incidence as reported in the original cohort.

The distribution of the PC data was such that 31 percent PC could be used to discriminate between the control and patient populations. Nineteen of the 23 schizophrenic patients, 9 of the 9 schizophreniform patients, but only 2 of the 15 control patients had PC values less than 31 percent. One of the two control subjects who showed the abnormality was a migraineur. The other control with a low PC level was a medical student with no apparent illness. Overall, these results

Table 1

Distribution of Erythrocyte Ghost Phospholipids in Controls, Schizophrenics, and Schizophreniform-Disorder Patients

Phospholipid	Control $N = 15$	Percent of Total Schizophrenia $N = 23$	Schizophreniform $N = 9$
Phosphatidylcholine	33.7 ± 1.2	29.3 ± 1.1*	28.7 ± 0.5*
Phosphatidylethanolamine	18.8 ± 1.5	17.1 ± 0.9	18.4 ± 1.2
Phosphatidylserine	15.4 ± 1.2	15.1 ± 1.0	15.9 ± 0.7
Phosphatidylinositol	3.1 ± 0.5	2.3 ± 0.2	2.3 ± 0.2
Ethanolamine Plasmalogen	10.3 ± 0.9	12.0 ± 0.9	11.9 ± 1.1
Sphingomyelin	19.7 ± 0.9	24.1 ± 1.5*	23.3 ± 1.8†

* - Significantly different from control, $p < 0.05$ (two-tailed)
† - Significantly different from control, $p < 0.05$ (one-tailed)

confirm the marked enrichment of the PC deficiency in schizophrenic populations found by others (Stevens 1972; Henn 1981). However, these results do not confirm the increase in PS to compensate for the loss of PC. The reason for this difference is not clear. The data suggest the need for interlaboratory verification of results and standardization of analytical techniques. The observation that a small percentage of controls (13%) gave a "false-positive" result indicates the need to evaluate an extensive and varied control population before it will be possible to use the membrane lipid abnormalities as a "blood-test" for schizophrenia.

Although the membrane abnormalities did not discriminate between schizophrenic and schizophreniform populations, the effect of lithium on erythrocyte ghost phospholipid methylation did discriminate between these groups. The kinetics of phospholipid methylation in erythrocyte ghosts in shown in Table 2. These data confirm the results of others (Hirata & Axelrod 1980) that methylation is probably catalyzed by two methyltransferases, inasmuch as the Km for [^{3}H] PME formation (0.92 uM) is distinctly different from that for [^{3}H] PDE (2.74 uM) and [^{3}H] PC (3.15 uM) formation. A concentration of 3 uM [^{3}H] S-adensoylmethionine (SAM) or approximately the apparent Km concentration for methyl-transferase-II was used in subsequent studies.

The data in Table 3 show the effect of lithium (0.5 and 1.0 mM) on phospholipid methylation in erythrocytes ghosts prepared from controls, schizophreniform-disorder patients, and schizophrenics. The lithium effects were highly individual. For example, in controls #1 and #3, lithium had relatively little effect on methylation while on control #2, lithium inhibited methylation, particularly the formation of [^{3}H] PME. In contrast, lithium markedly stimulated [^{3}H] PME formation in the schizophreniform patients, although the magnitude of the increase was quite variable, e.g., from 158 percent in Patient #2, to 646 percent in Patient #1. Lithium either inhibited or had no significant effect on phospholipid methylation in three schizophrenic patients. Although the sample is quite small, these data suggest that further study of the phospholipid methylation system as a potential site of lithium action is warranted.

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Table 2

Kinetics of Phospholipid Methylation in Human Erythrocyte Ghost Membranes*

Parameter**	[^{3}H]PME	[^{3}H]PDE	[^{3}H]PC
Km†	0.92	2.74	3.15
Vmax†	2.81	6.38	14.67

*Various concentrations of [^{3}H]SAM (.1 to 10 μM) were used to determine the kinetic plots. The methylated products were isolated by thin layer chromotography (Crews et al. 1980).

**The kinetic parameters, Km and Vmax, were determined as described by Wilkinson (1961).

†Km - μM; Vmax - p mol/mg protein/30 min.

Table 3

Effect of Lithium on Phospholipid Methylation in Controls, Schizophrenics and Schizophreniform-Disorder Patients*

Group	[Lithium] mM	Percent of Control (no added lithium) [^{3}H]PME	[^{3}H]PDE	[^{3}H]PC
Control #1	0.5	96	97	90
	1.0	93	97	93
Control #2	0.5	49	90	90
	1.0	32	74	60
Control #3	0.5	82	84	76
	1.0	103	103	101
Schizophreniform #1	0.5	300	23	105
	1.0	646	84	155
Schizophreniform #2	0.5	125	149	202
	1.0	158	214	214
Schizophreniform #3	0.5	225	98	139
	1.0	323	152	219
Schizophrenic #1	1.0	60	91	85
Schizophrenic #2	1.0	82	104	68
Schizophrenic #3	1.0	67	75	76

*Methylation was measured as described in the legend to Table 2 except that 3 μM [^{3}H]SAM was used in all experiments and various concentrations of lithium were added in vitro. All incubations were done at 37°C, pH = 8.0 and in the presence of 2 mM $MgCl_2$. Data are expressed as percent of the value obtained in the absence of lithium.

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Phospholipids and Phospholipid Methylation in Platelets and Brain

Donna Mandio Cordasco,[1] David Wazer,[1] David J. Segarnick,[1] Andrew Lautin, M.D.,[1] Arnold Lippa, Ph.D.,[2] and John Rotrosen, M.D.[1]

Recent studies of membrane phospholipid composition and metabolism indicate that phospholipids are integrally involved in regulating membrane biochemistry and biological signal transmission. In all biological organisms, bilayer membranes separate the intracellular cytosol from the extracellular environment and provide a supportive matrix within which numerous "membrane-bound" enzymes and proteins reside. Phospholipids are the major structural components of membranes, and synthetic phospholipids will spontaneously form membrane-like bilayers in aqueous media. In biological membranes (unlike artificial bilayers) the phospholipids are nonrandomly distributed between the two membrane leaflets. For example, in erythrocytes, phosphatidylcholine (PC) is primarily localized on the extracellular membrane surface, while phosphatidylserine (PS) is nearly all localized on the inner cytoplasmic membrane surface [these asymmetries are tissue-specific, e.g., in platelets PC is evenly distributed between the two membrane surfaces (Zwaal et al. 1977)]. Recent research indicates that phospholipid asymmetry effects cellular function by altering surface charge and membrane fluidity.

Certain aspects of membrane asymmetry are reflected in the enzymatic biosynthesis of (PC) through successive N-methylations of phosphatidylethanolamine (PE). Two enzymes catalyze this reaction sequence. The first enzyme which is located on the inner, cytoplasmic surface of the membrane synthesizes phosphatidyl-N-monomethyiethanolamine (PME) by adding one methyl group to PE. The second enzyme is located near the outer membrane surface and

[1]Psychiatry Service, Veterans Administration Medical Center, New York, NY 10010 and Department of Psychiatry, New York University Medical Center, New York, NY 10016.

[2]Lederle Laboratories, Division of American Cyanamid Co., Pearl River, NY 10965.

adds two additional methyl groups to PME to form phosphatidyl-N,N-dimethylethanolamine (PDE) and PC. S-adenosyl-L-methionine (SAM) is the methyl donor for both enzymes. In erythrocytes, the products of phospholipid methylation are asymmetrically distributed; PME is localized on the intracellular membrane surface while PDE and PC are on the extracellular surface (Hirata & Axelrod 1978). This product distribution is established through a flip-flop mechanism whereby PME is translocated through the lipid matrix and methylated to PDE and PC on the extracellular side of the bilayer. Associated with phospholipid methylation are localized changes in membrane fluidity, and receptor exposure (Strittmatter et al. 1979a), Ca^{++} ATPase activity (Strittmatter et al. 1979b), receptor-cyclase coupling (Hirata et al. 1979) and other membrane-mediated events.

Phosphatidylserine, a negatively charged phospholipid, is almost exclusively localized on the inner membrane leaflet in red blood cells (Zwaal et al. 1977); recent reports (Henn 1981) suggest that PS may play an important role in the etiopathology of schizophrenia. PS is unique amongst the phospholipids insofar as it has a number of "pharmacologic" effects when administered (in low doses) *in vivo* or (at low concentrations) *in vitro*. Amongst these are the following central nervous system (CNS) effects: PS causes a rapid increase in acetylcholine release in rat cortex (Mantovani et al. 1976), it increases levels of homovanillic acid in rat brain, and enhances norepinephrine turnover in rat hypothalamus (Toffano et al. 1978). A study by Stevens (1972) which has recently been replicated by Henn (1981), indicates that schizophrenics' red blood cells contain approximately 40 percent more PS and 10-15 percent less PE and PC than red blood cells from controls.

Preliminary work from our laboratory investigating phospholipid methylation and membrane phospholipid composition is described.

Platelet Phospholipid Methylation

Since platelets have many properties in common with monoaminergic neurons and are often used in psychiatric research as peripheral models of CNS biochemistry, the authors undertook to study the role of phospholipid methylation in the regulation of platelet function.

Phospholipid methylation was assayed by incubation of intact platelets with ^{3}H-methionine as previously described (Cordasco et al. 1981). Three major lipid extractable products—PME PDE, and PC were synthesized. Formation of these products was pH, time- and temperature-dependent, and saturable with respect to precursor concentration. As in other tissue types, platelet phospholipid methylation is sensitive to certain agents which elicit tissue-specific responses. Physiological concentrations of epinephrine, adenine, and thrombin inhibited formation of ^{3}H-methylated phospholipids. In some aspects, however, phospholipid methylation in platelets differs from that in other tissues.

Although phospholipid methylation is a minor pathway for PC biosynthesis, in leukocytes methylation derived PC comprises a discrete, highly active pool which is the primary source of free arachidonic acid released in response to chemoattractants (Hirata et al. 1979). In the interest of determining whether platelets also contain differentially active PC pools, platelet PC was labeled by incubation with ^{3}H-methionine, ^{3}H-choline, or ^{14}C-arachidonic acid and then stimulated arachidonic acid release with thrombin. PC synthesized from each of the three precursors was equally reduced by thrombin treatment indicating that in platelets, PC formed through methylation does not comprise a functionally distinct pool.

Table 1

Product Remaining After Phospholipase C Digestion (% of Control)

	3H-PME	3H-PDE	3H-PC
No Phospholipase C	100	100	100
Phospholipase C Incubated with Intact Platelets	60	74	66
Phospholipase C Incubated with Lysed Platelets	17	18	14

Phospholipase C digestion of 3H-PME, 3H-PDE, and 3H-PC in intact or osmotically lysed pre-labeled platelets. Values are expressed as % of control samples which were run with each assay and did not contain added phospholipase C.

A further distinction between phospholipid methylation in platelets and in other tissues lies in the distribution of tritiated PME, PDE, and PC between the cytoplasmic and extracellular membrane surfaces. Intact and hypotonically lysed platelets were enzymatically digested with phospholipase C to determine the localization of ^{3}H-methylated phospholipids (Table 1). The products of platelet phospholipid methylation were found to be equally distributed on the intracellular and extracellular membrane surfaces. The symmetrical distribution of methylation derived PC in platelets is compatible with a report by Zwaal et al. (1977), indicating that total platelet membrane PC is also symmetrically distributed (in contrast to asymmetrically distributed erythrocyte membrane PC).

Given the differences in the pharmacological and biochemical characteristics of phospholipid methylation in platelets and other tissues (including synaptosomes), the authors question whether studying platelet phospholipid methylation in psychiatric patients will be of value as a model of CNS function.

Synaptosomal Phospholipid Methylation

In erythrocytes (Hirata et al. 1979) and cultured astrocytoma cells (Strittmatter et al. 1979c), agonist stimulation of β-receptors increases phospholipid methylation. These findings and their potential implications in neuroscience have encouraged the authors to examine norepinephrine (NE) stimulation of synaptosomal phospholipid methylation.

The ability of NE to enhance phospholipid methylation was assessed in a crude synaptosomal preparation by the method of Crews et al. (1980). NE stimulation consistently increased chloroform extractable radioactivity by 100% - 200% initially suggesting that NE stimulated phospholipid methylation. In order to verify product identities, the authors chromatographed the extracts in three thin layer chromatography (TLC) systems and serially scraped the TLC plates. The serial scrapes revealed several large NE-stimulated peaks of radioactivity which could not clearly be attributed to 3H-PME, 3H-PDE, or 3H-PC but which chromatographed with these methylated phospholipids in some TLC systems.

Table 2

	Chromatography System		
	(1)	(2)	(3)
Product			
PME	+	+	–
PDE	–	+	–
PC	–	+	+

NE stimulation of phospholipid methylation as observed in three chromatography systems. + indicates NE stimulated increase in radioactivity co-chromatographing with authentic standards of PME, PDE, or PC.
Chromatography system key:
(1) = chloroform:propanol:propionic acid:water 4:6:2:1
(2) = chloroform:methanol:4N ammonium hydroxide 70:35:4
(3) = chloroform:acetone:methanol:acetic acid:water 10:4:2:2:1

When the results from the three chromatography systems are compared (Table 2), it is apparent that the NE induced stimulation does not consistently correspond to PME, PDE, or PC indicating that NE does not stimulate phospholipid methylation under the conditions studied. In an attempt to identify the NE-stimulated product or products, several methylated substances which were reasonable candidates were chromatographed in the three previously described chromatography systems (Table 3). A test-substance must co-chromatograph with a NE stimulated peak in each of the three systems for a positive correlation to be made. To date, no substance has met these criteria and the chloroform extractable, NE stimulated products have not been identified.

Phospholipid Methylation in Aging

Comparative studies of phospholipid methylation were undertaken in synaptosomes from young adult and aged rats. The process of phospholipid methylation alters membrane fluidity and also generates PC which can be metabolized to free choline (Blusztajn & Wurtman 1981). Since both membrane fluidity and cholinergic neurotransmission are altered during the aging process, the authors theorized that phospholipid methylations may either underlie these processes,

or be modified in a compensatory way in older animals.

Phospholipid methylation was assayed in cerebral cortical synaptosomes from 5- and 24-month-old rats. Accumulation of 3H-PME was significantly increased in the tissue preparation from the older rats, while 3H-PC was unaltered (Table 4). This data is in agreement with results of a similar study (Crews et al. 1981).

Erythrocyte Phospholipids in Schizophrenia

In clinical studies (similar to those presented in this session by Fritz Henn), we have investigated alterations in erythrocyte membrane lipid composition as a marker for schizophrenia. Henn has reported that schizophrenics' erythrocytes differ markedly from those of controls in the distribution of the major membrane phospholipids. Phosphatidylserine levels are elevated (40% > controls) while PE and PC levels are decreased (15% < controls). The authors' laboratory has initiated a pilot study attempting to replicate these findings. Preliminary data (Table 5) indicate that red blood cell membranes from schizophrenics do not differ significantly from those of controls in lipid composition. Discussions with Henn suggested that differences in methodology may account for the discrepancies between the authors' data and his. The authors have conducted a series of experiments employing Henn's extraction methods, but are still unable to identify any substantive differences between schizophrenics and controls.

Table 3

	Chromatography System		
	(1)	(2)	(3)
SAM	+	+	–
Methionine	–		
Epinine	–		
3-Methoxytyramine	+	+	–
Norepinephrine	–		
Epinephrine	–		
DL-alpha-linolenic acid	–		
Arachidonic acid	+	+	–
Linoleic acid methyl ester	+	–	–
Arachidonic acid methyl ester	+	–	–
Linolenic acid methyl ester	+	–	–
DL-normetanephrine	–	–	+
DL-metanephrine	–	–	+
DL-4-hydroxy-3-methoxy-mandelic acid	+	–	–
3-Methoxy-4-hydroxy-phenyl-glycol	+	+	–

Association of NE stimulated peaks with co-chromatographed substances is indicated as +. Chromatography systems are those described in Table 2.

Table 4

	Age (months)	
	5	24
SAM (0.7 μM)		
PME	25.0 ± 1.4	30.1 ± 1.2*
PC	19.9 ± 1.3	21.5 ± 1.2
SAM (200 μM)		
PME	89.0 ± 4.8	97.2 ± 6.5*
PC	197.2 ± 9.2	211.2 ± 11.9

Phospholipid methylation in rat cerebral cortical synaptosomes. Values are in femtomoles of 3H-CH3 groups incorporated into each phospholipid per mg. protein. (*$p < .02$)

Table 5

	Controls ($N = 14$)	Schizophrenics ($N =$)
PE	32.8 ± 1.5	31.8 ± 1.0
PC	34.1 ± 3.0	33.1 ± 2.6
SPM	23.8 ± 3.0	24.6 ± 2.1
PS	9.3 ± 2.2	10.5 ± 2.1

Phospholipids as % of total phospholipid in washed, lysed red blood cell membranes. PE = phosphatidylethanolamine, PC = phosphatidylethanolamine, SPM = spingomyelin, PS = phosphatidylserine

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Occurrence and Significance of Beta-Carbolines and Tetrahydroisoquinolines

Co-Chairs: **Bo. P. Holmstedt, M.D.**
Department of Toxicology
Karolinska Institutet
Stockholm, Sweden

and

Earl Usdin, Ph.D.
Neurosciences Research Branch
National Institute of Mental Health
Rockville, Maryland

Cellular Actions and Localization of Beta-Carbolines and Tetrahydroisoquinolines

Floyd E. Bloom, M.D.[1] and Jack D. Barchas, M.D.[2]

One of the more intriguing scientific issues in neuropharmacology is the hypothesis that novel metabolites of the monoamine transmitters norepinephrine, dopamine, or serotonin may be formed in the body during ethanol intoxication. In the test tube, it is abundantly clear that the metabolic product of ethanol, acetaldehyde, can condense with the catecholamine transmitters to form a class of chemical called tetrahydroisoquinolines (TIQs), and with serotonin to form the class of compounds termed tetrahydro-beta-carbolines. When these compounds are administered to animals, they have been shown to be very active in altering behavior, transmitter actions, and neuronal activity. In fact, some scientists have proposed that such compounds could underlie the addictive properties of ethanol. This view is based upon experiments in which rats that have received several injections of certain TIQs into their brains will then greatly increase their voluntary consumption of alcohol for many months afterwards. Unfortunately, this intriguing issue is also one of great controversy, and the arguments rage on two fronts: Are these compounds actually ever formed in the brain of humans or experimental animals in relationship to the alcohol they consume and, secondly, do the effects of these compounds help us understand either the basis for intoxication or the mechanisms by which certain individuals become dependent on alcohol?

In an attempt to come to some closure on the most controversial aspects of the biological significance of these elusive substances and their possible broader medical implications, an international workshop was held at the Salk Institute Alcohol Research Center on December 12 and 13, 1981, supported by a supplemental grant from NIAAA. The Workshop, organized by Drs. F. Bloom (Salk Institute), J. Barchas (Stanford University), E. Usdin (National Institute of Mental Health) and M. Sandler (Queen Charlotte's Maternity Hospital), brought together scientists from throughout the United States and Europe for an extensive discussion of the alleged endogenous compounds, their relationship to tissue ethanol content, and the possible actions that—if formed—could be produced in experimental animals. The proceedings of this meeting will be published later this year; the present report summarizes some of the highlights and critical points of the meeting.

The premiere question which faced the workshop was whether these compounds can actually be measured in the body of experimental animals or human subjects and, if so, whether the amounts measured can in any way be influenced by prior ingestion of alcohol. Molecules in tissue fluids or in extracts of homogenized tissues can be measured in many ways, and the methods vary

[1]The Arthur Vining Davis Center for Behavioral Neurobiology, The Salk Institute, La Jolla, CA 92037.
[2]The Nancy Pritzker Laboratory for Behavioral Neurochemistry, Stanford University Medical School, Stanford, CA 94305.

considerably in their accuracy and sensitivity. Among the most sensitive and specific of the available methods are determinations by mass spectrometry. When these methods are applied to the measurements of beta-carbolines, it has so far proven to be extremely difficult to detect them under conditions in which the chemical being measured can be rigorously documented to have arisen in the animal rather than in the test tube during extraction and preparation of the sample for measurements. Thus, while there are several published reports that beta-carbolines can be extracted from human urine, spinal fluid, or from platelets after ethanol exposure, it is difficult to rely strongly on such reports without convincing evidence that the already detected sources of contaminating aldehydes, and other sources of artifactual carboline formation, have wholly been eliminated. Furthermore, many at the workshop shared the view that even if beta-carbolines could be authenticated as endogenous constituents of urine or platelets, this is insufficient to document their endogenous occurrence in central or peripheral nervous tissue.

The most "negative" series of detection attempts were reported by Dr. T. Bosin, presently of Indiana University, who perfected his methodology in the Laboratory of Dr. Bo Holmstedt of the Karolinska Institute. In the course of these studies, Bosin and Holmstedt recognized that beta-carboline-like structures were arising during the preparation of the samples to be measured, and that to a large extent these artifactual formations far outweighed the beta-carboline that might have been present in the original tissue or biological fluid source. Important sources of these artifactually formed carbolines included covert formaldehyde and acetaldehyde contamination of even extremely pure reagents such as dichloromethane and chloroform, and the nitrogen gas used to dry the specimens. In some cases Bosin inferred that significant aldehyde contamination could even have existed in the distilled water supply. Although the absolute amounts of such contaminating aldehydes may be relatively small, the amounts of presumptive carbolines are already vanishingly small and, in the hands of Bosin, disappear completely when steps are taken to trap out the contaminants. A particularly perplexing contaminant was their discovery that the 5-HT source to be used as an internal standard was itself contaminated with carbolines.

Similar problems of internal chemical contamination contributing to the exogenous formation of beta-carbolines during sample preparation also led Dr. Kym Faull of Stanford University to conclude that he was unable to document the endogenous formation of any beta-carboline in rat brain except for tetrahydro-beta-carboline (THBC), and the maximum amount detectable here was less than 0.5 nanogram/brain. This group terms indoleamine-aldehyde condensation products tryptolines using a serotonin numbering system. Using a form of mass spectrometry (negative chemical ionization with capillary columns) that would have permitted detection at 100 picograms per sample or below, Faull could not find evidence for the carboline products of tryptamine with acetaldehyde, serotonin with formaldehyde or acetaldehyde, or 5-methoxytryptamine with formaldehyde. The Stanford group is very concerned about artifactual formation; however, THBC, if verified, could have important implications, as it would strongly suggest that tryptamine (from which THBC is formed by the addition of formaldehyde) could exist as a transmitter substance independently of 5-hydroxytryptamine, much in the same way that dopamine exists as a transmitter independently of norepinephrine. THBC was shown to be the most potent displacer of [H^3]-tryptamine in ligand binding studies reported to the workshop by Dr. K. Kellar (Georgetown University), and those data would support the possibility of a functionally independent tryptaminergic system.

On the other hand, Dr. Steve Barker (University of Alabama), also using GC/MS, detected extremely large amounts of carbolines (500-1000 nanogram/g) in the adrenal glands of singly housed rats, as well as in their brains (20-50 ng/g). Barker conjectured that his values were so high because the rats were under the stress of isolation; the amounts he measured were considerably lower, although well above his threshold for detection, in rats which were group housed. Dr. Olaf Beck, also of the Karolinska Institute, was able to confirm that beta-carbolines could be detected in the urine of rodents and humans, and that it could be elevated after a drinking episode. However, even in this case, Beck found it difficult to conclude that the carboline was formed *in vivo* from aldehyde byproducts of the alcohol metabolism. He favored instead the possibility that the carbolines may have arisen from dietary sources, in-

cluding the alcoholic beverages themselves, since foods such as cheeses and fruits, especially grapes, are known to have high carboline content.

A somewhat stronger case was developed for the natural occurrence of aldehyde condensation products of the catecholamines. In this case, the resulting TIQs have been more reproducibly documented in tissue and body fluid extracts, and have been shown to be elevated further by recent alcohol ingestion. This body of evidence was comprehensively summarized by Dr. Mike Collins of Loyola University, Chicago, and by Dr. Gerald Cohen, of Mt. Sinai Hospital Medical School, New York. Dr. Birgitta Sjoqvist of the Karolinska Institute pursued the question of whether the particular TIQ which she was able to measure in the urine and cerebrospinal fluid (CSF) of non-alcoholic humans and in higher amounts in urine and CSF of acutely intoxicated humans, originated in the central nervous system; she measured TIQs in postmortem brain specimens from alcoholic and control subjects. Her results indicated that TIQs were detectable in amounts of 20-50 ng/g in dopamine-rich regions such as caudate and putamen, as well as in regions with much less dopamine, such as cerebral cortex and hippocampus. In general, the levels were 5 to 10-fold lower in control (non-alcoholic subjects) and in alcoholics who had died while sober for at least 2 weeks, although underlying neuropathologic consequences of the long-term alcoholism, which reduced endogenous dopamine and increased the content of its metabolite, homovanillic acid, may have contributed to the differences.

On the other hand, attempts by Drs. T. Shier and L. Koda (Salk Institute) to show the formation of DA-related TIQs in the brains of normal or ethanol intoxicated rats by following products formed from intraventricularly injected [H^3]-dopamine, failed to detect any known TIQ, with a method capable of detecting femtomolar amounts. Taken at face value, however, the data from human and some animal studies (summarized by Collins, and by M. Hirst, University of Western Ontario) would certainly be compatible with the view that TIQs may arise normally during catabolism of dopamine or norepinephrine, even without ethanol, and that larger amounts can be formed in the presence of alcohol, perhaps through the classical non-enzymatic condensation reaction of Pictet-Spengler. Dr. Virginia Davis (Veteran's Administration Hospital, Houston, Texas) presented the observations which had led her to hypothesize that tetrahydropapaveroline (THP) might also arise in a similar fashion by condensation of dopamine and dopa-acetaldehyde during dopamine metabolism in the presence of ethanol, but no new data documenting the occurrence of THP in brain or body fluids were presented.

Theoretical calculations by Dr. Henry Weiner (Purdue University) based upon known amounts of catecholamines and known rates of metabolism, and theoretical yields for the condensation reaction conditions which would exist *in vivo*, suggested that conclusive proof that beta-carbolines and TIQs did not exist may be difficult to obtain given that the maximum amounts which could be found could still be below the minute levels towards which the chemists had pushed the levels of detectability. A provocative idea, which appeared at least partially supported by existing data, was the possibility raised by Dr. A. Brossi (National Institutes of Health, Bethesda, Maryland) that TIQs arose not from acetaldehyde dopamine condensations, but rather from pyruvate-dopamine condensations in which oxidative decarboxylation lead to quinoline formation. If this suggestion could be validated, it might answer the unsettled puzzle of how measurable TIQs could be found when acetaldehyde remains below detectable levels.

The Workshop then turned its attention towards possible biological effects which beta-carbolines and TIQs might mediate. The majority of such studies were based on characterizing the pharmacological actions of synthetic carbolines and TIQs, while overlooking—at least for the moment—the critical issue of endogenous formation and its relevance to ethanol intoxication. In fact, several series of interesting biological actions were reported, but it is critical to realize that all such actions required doses of carbolines or TIQs which are orders of magnitude greater than even the most optimistic endogenous measurements.

The workshop participants heard a broad range of observations reported which indicated that synthetic TIQs and carbolines could exert actions at almost every step of monoaminergic function, including interactions with monoamine transmitter ligand binding sites (K. Kellar, Georgetown University, Washington, D.C., and Y. Nimit, VA Hospital, Houston, Texas), possible en-

dogenous inhibitors of monoamine oxidase (M. Sandler, Queen Charlotte's Maternity Hospital, London), and monoamine transmitter synthesis rates (R. Bruce Holman, University of Redding, U.K., and Dr. C. Coscia, St. Louis University) as well as benzodiazepine binding sites (K. Braestrup, A/S Ferrosan, Roskilde, Denmark, and S.M. Paul, NIMH, Bethesda, Maryland), and benzodiazepine actions on sleep stages (W. Mendelson, NIMH, Bethesda, Maryland).

Many of the pharmacological studies of beta-carbolines and TIQs could be viewed as tests of the general hypothesis that addictive or reinforcing properties of ethanol could be mediated by an ethanol-derived condensation product, and the related subhypothesis that such products produced their effects by interaction with one of the endogenous opiate peptide systems.

At the level of single neurons, a strong case for such relationships was established by G. Siggins (Salk Institute) who reported that synthetic salsolinol and 7-methoxy salsolinol (the TIQ formed from dopamine and acetaldehyde) applied by micro-iontophoretic methods, and ethanol, applied by micro-pressure pulse ejection tended to affect neuronal discharge in various brain regions with a qualitative pattern similar to the effects of opiate peptides in these same regions. In general, all compounds were inhibitory in all regions except hippocampus, where all produced excitatory actions. Furthermore, many of the opiate like excitatory responses of hippocampal neurons to ethanol or salsolinal could be antagonized by parenteral or locally applied opiate antagonists. However, the TIQ and ethanol effects were also antagonized by the cholinergic receptor antagonist scopolamine, suggesting that the sites at which TIQs are able to elicit effects are not restricted to endogenous opiate receptors. It is possible that the TIQs, opiates, and ethanol share common actions through an ion channel effect, such as the changes in transmembrane Ca movements described by D. Ross (University of Texas Medical School, San Antonio, Texas).

At the level of the behaving animal, an intriguing set of data which furthered the uncertain linkage between TIQ effects and endogenous opiates was presented by H. Altshuler (TRIMS, Houston, Texas). After laboriously training rats in a two-way drug discrimination task (in which animals reliably gave one response when injected with low intoxicating doses of ethanol and another response when injected with saline), Altshuler investigated the degree to which rats could generalize (or discriminate) their response to potentially related drugs. For example, neither ethanol nor THP (when injected into the cerebroventricles) could produce an effect interpreted by the rats as "like intraperitoneal ethanol"; likewise, acetaldehyde injected either into the cerebroventricles or intravenously was also interpreted as "not alcohol." However, the injection of 50 ng doses of salsolinol intracerebroventricularly was generalized as alcohol-like, and this effect could be antagonized by the opiate antagonist naltrexone. In a conceptually related experiment, Altshuler also reported that he had been able to train some baboons to self-administer oral ethanol and, in a well-balanced control series of animals, he had observed the ethanol self-administration was significantly diminished by naltrexone or another opiate antagonist, naloxone. However, the doses are higher than those required to antagonize injected opiates.

It was, of course, evident to all those at the workshop that a very controversial series of ethanol self-administration experiments had fanned the embers of the various carboline-TIQ hypotheses of ethanol dependence at a time when strong supportive data in the central nervous system had been lagging. Those experiments, reported in the early 1970s by R.D. Myers and his colleagues (*see* Myers 1980; Dietrich & Erwin 1980; Melchior & Collins 1982) indicated that intracerebroventricular injections of THP and certain other TIQs could cause permanent increases in voluntary alcohol ingestion in rats. Although there have been some replications of the basic observation, the original phenomenon has proven to be far from reproducible even when rat species, strain, injection technique and evaluation methods are followed stringently. Furthermore, J.D. Sinclair (Alko, Finland) reported at the workshop that when he and Myers attempted to replicate this experiment together in the Myers' laboratory, they were unable to replicate the THP effect reported previously, although some rats given infusions of beta-carbolines did show modest increases in ethanol ingested.

Dr. Z. Amit (Concordia University, Montreal) reported that he had been unable to replicate the enhancement of ethanol ingestion in rats with any carboline or TIQ, but that he had been able to demonstrate to his own satisfaction that rats

would self-administer salsolinol intravenously. However, even rats which exhibited salsolinol self-administration would not accept ethanol as a substitute nor consume significant amounts of oral ethanol. Dr R. Dietrich (University of Colorado Alcohol Research Center, Denver, Colorado) reported that he and his colleagues had in part replicated the THP effect on increased ethanol consumption, but noted that the amounts of ethanol ingested were in general quite modest, generally less than 5 g/kg/day. Others noted that rats which seemed to give the greatest increase in consumption were those with lower initial intake before drug infusion; after the THP treatments the levels consumed by these rats then approached the levels consumed by uninjected controls.

Dr. C. Melchior (University of Illinois Medical Center, Chicago, Illinois) who had participated in the original Myers experiments turned her attention in the interim to the possible interactions between the development of ethanol tolerance and the importance of environmental cues, in order to confront more directly the possibility that such cues could help to distinguish physiological factors which regulate the development and expression of tolerance. In these experiments, mice were trained by receiving daily injections of various doses of ethanol in one laboratory setting with distinctive lighting and sensory cues, and then subsequently tested for the hypothermic effects of a test dose of ethanol either in the training environment or in a novel testing environment. A purely metabolic effect of prior ethanol injection was ruled out in a separate group of mice who were exposed to the same training environments but received their ethanol only in their home cages. Although some tolerance developed in all mice, hypothermia was much less pronounced (i.e., tolerance was greatest) in those mice tested in their training environments. In an extension of these studies, Melchior also observed that injection of 3-carboxyl salsolinol or THP could regulate this process, appparently preventing the development of tolerance by diminishing, through an unknown mechanism, the brain ethanol content in response to the test i.p. dose. She then linked this effect to the earlier reports on THP increasing ethanol consumption by suggesting that one effect of the THP could be to inactivate normal adaptive mechanisms which would normally act to suppress ethanol consumption, perhaps by interfering with the release or effects of some natural transmitter system.

This workshop helped to crystallize certain important open issues which must be experimentally settled before it can be stated that any carboline or TIQ mediates an action of ethanol. The primary open issue is the establishment of the formation of these compounds *in vivo* in nervous tissue in any system in which the formation can be shown to be linked to ethanol content of the tissue, rather than to an artifact of the measuring methods. The evidence available at the time of the workshop seemed to most observers to favor the interpretation that the existence of carbolines under verified uncontaminated conditions was doubtful. The evidence was somewhat more convincing that TIQs formed in brain without ethanol and were increased after long-term ethanol exposure.

The next major open issue was whether the effects ascribed to injections of hundreds of nanograms of these compounds could be considered relevant to the issue of whether if formed endogenously in picogram amounts their release and actions could in any way be shown to be analogous to the effects of the ethanol. Again, the data presented were intriguing and interesting, but far from comprehensive and reproducible. Several actions of TIQs, those on single neurons and those on animals exhibiting one or another effect of ethanol, seemed to be generally similar and antagonized by opiate antagonists. At the same time, a variety of transmitter ligand binding sites were also found to be capable of weak interactions with synthetic carbolines and TIQs.

A third open issue centers on the interpretation of the relatively low doses of ethanol ingestion which some investigators have been able to observe after central injections of TIQs or after other drug treatments. Some held that any treatment that will cause experimental subjects to increase their consumption of ethanol is interesting if the phenomenon to be studied is defined as the basis for ethanol consumption. Others took the view that the critical phenomenon to be studied is the intoxicating and reinforcing pharmacological actions of ethanol which require detectable blood and tissue alcohol levels. Under the latter view, experimental perturbations which increase ethanol consumption above baseline but not far enough above to give detectable blood alcohol levels may be dependent upon totally different mechanisms than those which maintain excessive alcohol consumption in humans.

These three major open issues then can be

distilled to one final important question: Given the rather marked disparity between the observed endogenous levels of these substances and their pharmacologically effective concentrations, is it possible to conceive of circumstances in which the necessary pharmacological levels could be attained and measured in a discrete locale, like a synaptic cleft? Although this and other solid issues offer an attractive hypothetical motivation for further research, it seems likely that the will-of-the-wisp nature of these pharmacologically potent substances is likely to persist for some time. Solution to these open questions would, however, be of important benefit to the explanation of problems of alcohol and opiate abuse.

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Endogenous Opioid Mechanism in Neuroendocrine Regulation in Normal and Psychopathological States

Co-Chairs: **David S. Janowsky, M.D.**
Department of Psychiatry
University of California
School of Medicine
La Jolla, California

and

S. Craig Risch, M.D.
Department of Psychiatry
University of California
School of Medicine
La Jolla, California

The Effect of a Methadone Challenge on the Prolactin and Growth Hormone Responses of Psychiatric Patients and Normal Controls

Lewis L. Judd, M.D.[1,2] S. Craig Risch, M.D., [1,2] Donal C. Parker, M.D.,[3] David S. Janowsky, M.D.[1,2] David S. Segal, Ph.D.,[1] and Leighton Y. Huey, M.D.[1,2]

The endogenous opiate-like peptide systems appear to be implicated in a number of important behavioral and physiological functions. The authors, like others, have been interested in the potential role endorphins may play in the pathophysiology of major psychiatric disorders. Based on previous studies, the authors hypothesized that a potentially important interrelationship may exist between the endogenous opioid peptide systems, specific neuroendocrine regulatory factors, and affective disorders (Judd et al. 1981, in press).

[1]Department of Psychiatry, School of Medicine, University of California, San Diego, La Jolla, CA 92093.
[2]Psychiatry Service, San Diego VA Medical Center, La Jolla, CA 92093.
[3]Department of Medicine, School of Medicine, University of California, San Diego, La Jolla, CA 92093 and Medical Service, San Diego VA Medical Center, La Jolla, CA 92093.

Address reprint requests to Dr. Lewis L. Judd, Department of Psychiatry (M-003), School of Medicine, University of California, San Diego, La Jolla, CA 92093.

Endorphins are involved in the regulation of two neurohormones which have been reported to be abnormal in some depressed patients; these are prolactin (Gold et al. 1978; Judd et al. 1981) and growth hormone (Koenig et al. 1980; Meites et al 1979; Shaar et al. 1977). There have been conflicting reports in the literature on prolactin levels in depression, but Asnis et al. (1980) and Linkowski et al. (1980) have reported lower basal prolactin levels in depressed patients. In addition, Linkowski et al. (1980) and Extein et al. (1980) both reported blunted prolactin responses to respective challenges of thyrotropin-releasing hormone (TRH) and morphine in depressive disorders.

It has also been reported that growth hormone responses to various provocative agents are blunted in depression. Specifically, growth hormone responses to L-DOPA, insulin-induced hypoglycemia, and to amphetamine—all potent stimulators of growth hormone release—are absent or diminished in depressed patients (Sachar et al. 1975; Langer et al. 1976).

Here we report the results of a methadone challenge on prolactin and growth hormone responses in a diagnostically mixed sample of psychiatric patients and normal controls.

Method

Forty-one medically healthy male psychiatric inpatients and normals participated in the study after completing informed consent procedures. The patients' research diagnoses were derived by

the Schedule for Affective Disorders and Schizophrenia-Research Diagnostic Criteria (SADS-RDC) method, and were based upon independent agreement of two psychiatrists. There were four experimental groups as follows: Schizophrenics, $N = 8$, age range 23-45 years, mean age 31.1 years; Manics, $N = 6$, age range 22-46 years, mean age 34.2 years; Depressive Disorders, $N = 16$, age range 22-54 years, mean age 35.86 years; Normal Controls, $N = 11$, age range 22-32 years, mean age 24 years. Subjects were drug-free at time of testing, with the patients having been removed from all psychoactive agents 7 days prior to the experimental sessions. It should be noted that several subjects required single doses of phenothiazines for clinical management a day or two preceding the experiment. Sessions began at 9:00 a.m. with the placement of a heparinized intravenous catheter to which the subjects were allowed 30 minutes for accommodation. Following this, blood samples were drawn once at baseline and at 30 and 60 minutes following the administration of 10 mg intramuscular (i.m.) of methadone-HCl. All the samples were assayed in duplicate within the same assay and blindly by those performing the assay (Parker et al. 1973).

Results

The results of the prolactin assay are included in Table 1. As anticipated, methadone increased prolactin secretion for the entire subject sample from a mean baseline level of 11.7 ± 1.5 ng/ml to a peak of 27.5 ± 5.25 ng/ml at 60 minutes post methadone ($t = 2.78$, df = 40; $p < 0.01$). Methadone induced a mean prolactin rise of approximately two- to three-fold over baseline levels in all four groups of subjects. There were, however, significant differences between the groups in both the baseline levels and in the net prolactin response to methadone. The depressive disorder patients stood out by having a significantly lower mean basal prolactin level ($p < 0.05$) than was observed in the other three groups of subjects. Further, the depressed patients had significantly lower mean levels in both 30 ($p < 0.01$) and 60 ($p = 0.01$) minute samples as compared to the schizophrenic, manic, and normal groups who responded to methadone with a much more marked and robust increase in prolactin.

An examination of the raw data revealed that eight of sixteen (50%) of the depressed patients had absent or very attentuated prolactin responses to methadone, while the remaining eight manifested prolactin increases. When a blunted prolactin response was defined by a rise of less than 2 ng/ml in either 30 or 60 minute samples, then eight depressed patients and two normals had blunted responses.

The mean growth hormone levels for the four experimental groups are presented in Table 2. As can be seen, methadone significantly increased the mean growth hormone levels in all four groups of subjects over baseline levels. It rose from a mean of 3.02 ± 1.34 mIU/ml at baseline to a high of 20.55 ± 9.66 mIU/ml at 60 minutes ($F = 12.03$; df = 40; $p < 0.05$). Although no

Table 1

Mean Serum Prolactin Levels (Ng/Ml) at Baseline, 30, and 60 Minutes Post-methadone (10 Mg) in the Three Psychiatric Patient and the Normal Control Groups

	Baseline	30 minutes	60 minutes	Δ Baseline to 60 minutes
Schizophrenics ($N = 8$)	15.9 ± 3.6	33.1 ± 9.4	42.0 ± 10.9	26.1
Manics ($N = 6$)	13.0 ± 4.5	30.8 ± 12.9	34.4 ± 13.5	21.4
Depressed ($N = 16$)	7.5 ± 0.9	10.6 ± 1.9	15.4 ± 3.5	7.9
Controls ($N = 11$)	14.1 ± 3.2	25.5 ± 6.3	30.6 ± 7.7	16.5
Mean for Entire Subject Sample	11.7 ± 1.5	21.9 ± 5.0	27.5 ± 5.3	15.8

Kruskal-Wallis One-Way ANOVA

Group Difference at Baseline $H = 10.09$; df 3; $p < 0.05$
Group Difference at 30 Minutes $H = 12.7$; df 3; $p < 0.01$
Group Difference at 60 Minutes $H = 10.8$; df 3; $p < 0.01$

statistically significant differences emerged in growth hormone response in regard to diagnosis, there was evidence that the manic and depressed patients responded to methadone with a less marked increase in growth hormone in the 30- and 60-minute serum samples than did the schizophrenic and normal control groups. An examination of the raw data revealed that ten of thirteen depressed patients and five of seven manic patients had blunted growth hormone responses to the methadone challenge. However, three of seven patients in the schizophrenic and four of eleven in the control group also had blunted growth hormone responses. Thus, the blunted growth hormone responses did not occur as exclusively among the depressive disorder patients as was seen with the blunted prolactin response.

Eleven of the thirteen depressed patients for whom both growth hormone and prolactin data were available manifested either a blunted prolactin or growth hormone response or both to the same methadone challenge.

Discussion

Before discussing the data, which were derived under these experimental conditions, there are some issues potentially affecting the data which should be mentioned. One manic and two schizophrenic patients required single p.r.n. (as needed) doses of phenothiazine during the time they were on "drug-free" status. This slightly increased the baseline prolactin levels in these three patients, which in turn had an effect on the mean basal levels for the experimental groups of which they were members. There are reports that attenuated prolactin responses have been observed in subjects who are relatively hyperprolactinemic, but this was not manifested in these three patients, since each had robust prolactin increases following the methadone administration.

Another issue deserving of comment is the fact that the age range in the control group was lower and therefore not comparable to the three patient groups. This is an acknowledged flaw in the design, but on the other hand this should not affect the results presented here. Specifically, there is no evidence that age per se, at least within the range studied here (i.e., 21-54 years), would have any effect on either basal levels or upon the response to challenge agents of prolactin or growth hormone.

The mean basal prolactin level in the depressed patients was significantly lower than it was for the manic, schizophrenic, and control groups. Because the p.r.n. phenothiazine administration slightly increased the mean basal prolactin levels in the manic and schizophrenic groups, it is not our intention to highlight this particular finding, other than to mention that it is consistent with the reports by Asnis et al. (1980) and Linkowski et al. (1980), both of whom reported lower basal levels in depression. The blunted prolactin response to methadone we observed in eight of sixteen depressed patients is consistent with the findings of Linkowski et al. (1980) and Extein et al. (1980) who observed the same response from the challenges of TRH and morphine, respectively.

Table 2

Effect of Methadone-HCl (10 Mg Im) on Growth Hormone (mIU/Ml) In Psychiatric Patients and Normal Controls

	Baseline	30 Minutes	60 Minutes
Schizophrenics ($N = 7$)	2.53 ± 0.51	17.60 ± 14.10	46.29 ± 25.43
Manics ($N = 7$)	3.18 ± 0.89	6.17 ± 3.88	9.43 ± 5.40
Depressed ($N = 13$)	4.80 ± 2.90	4.19 ± 1.49	11.36 ± 5.43
Normals ($N = 11$)	2.09 ± 0.53	21.11 ± 9.96	22.15 ± 7.48
Mean for Entire Subject Sample	3.02 ± 1.34	12.46 ± 4.29	20.55 ± 9.66

Kruskal-Wallis One-Way ANOVA

Group Difference at Baseline	N.S.
Group Difference at 30 Minutes	N.S.
Group Difference at 60 Minutes	N.S.

There is clear evidence that methadone significantly increased the mean growth hormone secretion in the entire subject sample. Whereas there are reports in the literature indicating that opiate/opioids stimulate growth hormone secretion in animals (Meites et al. 1979; Shaar et al. 1977; Koenig et al. 1980), this is the first report of which we are aware reporting an opiate-induced growth hormone rise in normal subjects and in psychiatric patients. There were no significant group differences in the mean growth hormone response following methadone. Blunted growth hormone responses were present in subpopulations in each of the three patient groups and in the normal controls as well. Of specific interest was the fact that the majority of the patients in both the manic (five of seven) and the depressed (ten of thirteen) groups had blunted growth hormone responses to methadone. While the blunted growth hormone response did not occur exclusively in the affective disorder patients, it was predominantly manifested in these patients.

It is intriguing that eleven of the thirteen depressed patients, on whom we have both prolactin and growth hormone data, manifested blunting of prolactin or growth hormone or both to the same opiate challenge.

It is possible that the blunted prolactin and/or growth hormone response may be an additional neuroendocrine dysfunction that is correlated with the presence of affective disorder (e.g., depressive disorders). It is also possible that this neuroendocrine dysfunction may prove to be a useful diagnostic marker for the identification of this group of psychiatric disorders.

These findings are consistent with our original hypothesis that a potentially important interrelationship exists between the opioid peptide systems, certain neuroendocrine regulatory factors, and the pathophysiology of affective disorders. The exploration and characterization of this relationship continues to be a promising direction for future research.

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Response of Plasma Cortisol and β-Endorphin Immunoreactivity to Surgical Stress

David Pickar, M.D.,[1] Martin R. Cohen, M.D.,[1] Michel Dubois, M.D.,[2] and William E. Bunney, Jr., M.D.[3]

Introduction

Considerable data now exist from animal experimentation that the endogenous opioid system plays an important role in the biological response to stress and in endogenous analgesic mechanisms (Amir et al. 1980; Rossier et al. 1980; Madden et al. 1977). Several lines of evidence support the notion that the endogenous opioid system is involved in pain perception in humans. Stimulation of the periaqueductal gray area in chronic pain patients has been shown to produce both analgesia and increased CSF levels of opioids (Hosobuchi 1977; Akil et al. 1978), while profound and long-lasting analgesia has resulted from the intrathecal administration of β-endorphin (Oyama et al. 1980). Naloxone-reversible stress-induced analgesia has recently been demonstrated to occur clinically (Willer et al. 1981). The relationship between stress and behaviors such as pain perception are, however, complex (Antelman & Cagguilla 1980) and biologic responses are known to vary with stress paradigm (Mason 1975) and with individuals (Naber et al. 1981).

The authors have used general surgery as a paradigm for studying stress effects on circulating levels of plasma β-endorphin immunoreactivity and cortisol in humans and for investigating relationships between pain perception and hormone levels.

Method

Nine adults (seven males, two females; ages 18-60) who underwent laparotomies as part of a National Cancer Institute protocol for the assessment of testicular or ovarian malignancy were studied. Patients were medication-free for at least 72 hours prior to surgery and were free of medical complications other than regional malignancy. Pre-medication was with pentobarbital (100 mg, i.m.) and anesthesia was induced with thiopental and muscle relaxant. No opiates were given until the 1st-3rd postoperative hour when the patient was awake, at which time morphine sulfate (1.5-3.5 mg/hr i.v.) was administered as needed (patient request) for relief of postoperative pain.

Plasma was collected from each patient prior to intubation and anesthetic induction, 10 minutes after skin incision, and at 30-minute intervals during surgery until skin closure. In six of the nine patients plasma was also collected immediately after intubation and during the period of postoperative morphine administration. Plasma assay for β-endorphin included antiserum prepared from rabbits against synthetic human β-endorphin and demonstrates by weight <50 percent cross-reactivity with β-lipotropin, <0.01 percent with α-endorphin and α-MSH, <0.004 percent with leu- and met-enkephalin and <5 percent with ACTH.

Results

Anesthesia induction did not significantly effect either plasma β-endorphin (ir) or plasma cortisol: pre-induction means ± SEM were 20.5 ± 2.9 pmole/liter and 23.7 ± 2.5 μg percent and post-induction means ± SEM were 26.9 pmole/liter and 26.1 ± 4.2 μg percent, respectively. In contrast, surgery was associated with significant increases in both variables (Figure 1). These elevated levels typically persisted throughout the surgical procedure and, in some patients, plasma β-endorphin (ir) increased still further upon awakening from anesthesia. Morphine administration was associated with significant decreases in both plasma cortisol and β-endorphin (ir) (Figure 2).

The authors used the total amount of morphine administered over the first 24 postoperative hours as an objective assessment of the degree of subjects, postoperative pain. Total morphine requirement was related to patient age ($r = -.69$, $p < .05$) and patient weight ($r = .55$, $p < .1$), find-

[1]Neuroscience Branch, National Institute of Mental Health, Bethesda, MD 20205.
[2]Department of Anesthesia, National Institutes of Health, Bethesda, MD 20205.
[3]Department of Psychiatry and Human Behavior, California College of Medicine, University of California at Irvine, Irvine, CA 92717.

ings consistent with known morphine pharmacokinetics. Neither age nor weight, however, were significantly related to mean surgery levels of β-endorphin (ir) (Table). Mean surgery levels of plasma β-endorphin (ir) were negatively correlated with total morphine requirement (Figure 3), while those of plasma cortisol showed a similar tendency ($r = -.65$, $p < .1$). Presurgery cortisol levels were significantly related to mean surgery cortisol levels ($r = .85$, $p < .01$).

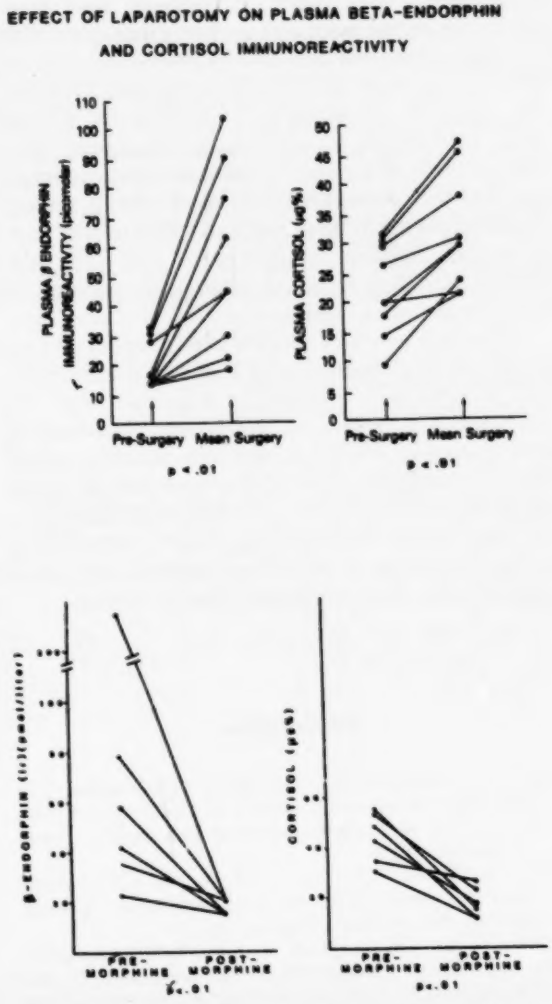

FIGURE 2. The effect of postoperative morphine on levels of plasma β-endophin (ir) and cortisol in six patients. Samples were collected after patients awoke from anesthesia but before postoperative analgesics and during morphine administration.

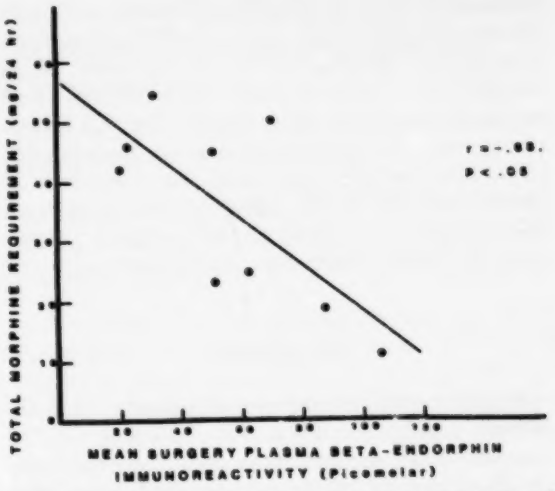

FIGURE 3. Correlation between mean surgery levels of plasma β-endorphin (ir) and total amount of morphine administered during the first 24 postoperative hours (1.5-3.5 mg/hr, i.v.)

Table

Patient Demography, Levels of Plasma β-Endorphin Immunoreactivity, and Post-Operative Morphine Requirements

Patient No.	Age	Weight (kgs)	Pre-surgery β-endorphin (ir) (picomolar)	Mean Surgery β-endorphin (ir) (picomolar)	Morphine Requirement* (mg/24 hr)
1	21	75.4	< 14.4	62.4	24
2	30	72.5	< 14.4	22.5	46
3	41	82.7	31.0	91.1	18
4	59	57.5	28.2	45.0	22
5	60	47.5	32.6	103.7	12
6	16	67.3	16.0	76.2	50
7	21	63.0	< 14.4	30.4	56
8	28	81.0	< 14.4	17.4	44
9	43	85.5	< 14.4	45.0	45

*mg per 1st 24 post-operative hours
Age vs Morphine Requirement: $r = -.89$, $p < .05$
Weight vs Morphine Requirement: $r = .55$, $p < .1$
Mean Surgery Plasma β-endorphin (ir) vs Morphine Requirement: $r = -.88$, $p < .05$

Because plasma β-endorphin (ir) levels prior to surgery were often lower than the sensitivity of our assay, no parametric testing of a correlation between these levels and postsurgical morphine requirement could be made. It was possible, however, to divide the patients into groups on the basis of data distribution (Table): six patients with low plasma β-endorphin (ir) levels (< 17

picomolar) prior to surgery and three with high plasma β-endorphin (ir) (≥28 picomolar). Similarly, morphine requirements were distributed biomodally: high requirements, 44-56 mg, and low requirements, 12-24 mg. All six patients with low presurgery plasma β-endorphin (ir) levels required high morphine doses and all three patients with high levels of plasma β-endorphin (ir) required low morphine doses ($p < .05$, Fisher Exact Test, two-tailed).

Discussion

Surgical stress proved to be a potent stimulator of both plasma cortisol and β-endorphin (ir). In contrast to the surgical stress itself, plasma levels of β-endorphin (ir) and cortisol were not significantly effected by anesthesia induction. Although this latter finding lends little support for an involvement of the endogenous opioid system in anesthesia effects, it does not exclude a role for brain opioids, whose contents have been shown to vary independently from pituitary β-endophrin (Rossier et al. 1977), or for other circulating opioids, in the mediation of anesthetic effects. The parallel cortisol and β-endorphin (ir) increases during surgical stress also support the close association between β-endorphin (ir) and the hypothalamic-pituitary-adrenal (HPA) axis (Mains et al. 1977; Guillemin et al. 1977; Vale et al. 1981). The marked decrease in both cortisol and β-endorphin (ir) associated with postoperative morphine administration suggests the possibility of a common feedback inhibition by opiates. It is also possible, however, that decreases in these neurohormones may relate to decreased conscious pain perception produced by morphine.

The wide individual differences in subjects, postoperative morphine requirements are consistent with clinical belief. This variance was in part explained by pharmacokinetic considerations such as relationships with age and body weight, and by non-pharmacokinetic variables such as plasma levels of β-endorphin (ir). Multiple regression analysis of patient age and mean surgery plasma β-endorphin (ir) increased the degree of variance predicted to 70 percent. Age and mean surgery plasma β-endorphin (ir) were individually able to predict 46 and 48 percent, respectively. Although this increase in variance predicted did not reach statistical significance, it does suggest the possibility that age and plasma β-endorphin (ir) may relate independently to postoperative morphine requirement.

The similar, although not quite as strong, negative correlation between stress-induced cortisol levels and postoperative morphine requirement may support a hypothesized link between human arousal and analgesia. Furthermore, the negative relationship between plasma β-endorphin (ir) prior to surgery and postoperative morphine usage suggests that variability in physical trauma may not be the major determinant of variance in postoperative pain. Rather, the patient's physiological response or arousal prior to surgery, which may be dependent upon the intensity of psychological stress and/or simply the innate responsiveness of the patient's arousal systems, seems to be a major determinant of postoperative analgesic requirement and may also predict the degree of physiological response to surgical stress.

Although levels of plasma β-endorphin (ir) are in actuality a composite of levels of β-endorphin and β-lipotropin, the results suggested that this complex may relate to important physiological processes. It is doubtful, however, that the plasma levels detected are, in and of themselves, sufficient to produce significant analgesia. More likely, these levels of circulating plasma β-endorphin (ir) reflect a central nervous system arousal which may involve the endogenous opioid system.

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Elevated Plasma β-Endorphin Concentrations in Depression and Cholinergically Supersensitive Release Mechanisms[1]

S. Craig Risch, M.D.,[2] David S. Janowsky, M.D.,[2] Lewis L. Judd, M.D.,[2] and Leighton Y. Huey, M.D.[2]

Morning plasma concentrations of beta-endorphin immunoreactivity were significantly higher in a group of depressed patients meeting the Research Diagnostic Criteria for Major Depressive Disorder or Schizoaffective Disorder, depressed, than in age- and sex-matched groups of normal controls and psychiatric patients without affective disorders. Furthermore, physostigmine stimulated release of beta-endorphin immunoreactivity was also significantly greater in the depressed patients. These results provide the first evidence for elevated plasma concentration of beta-endorphin in depression and also represent further evidence for cholinergic supersensitivity in depression. These results suggest that elevated plasma concentrations of beta-endorphin and cholinergically stimulated hypothalamic-pituitary beta-endorphin release, might potentially represent biological state or trait markers for depression.

Introduction

Adrenal cortisol hypersecretion, as well as flattened cortisol circadian periodicity, and failure to suppress plasma cortisol concentrations with the overnight low-dose dexamethasone suppression test, occur in a significant number of endogenously depressed patients, and have now been well established as substantive neuroendocrine markers highly specific for primary affective disorders (Stokes et al. 1975; Brown 1979; Carroll et al. 1976a, 1976b, 1981; Sachar 1976; Sachar et al. 1980a; Schlesser et al. 1980). Many investigators also believe that this neuroendocrine abnormality reflects limbic-hypothalamic-

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[2]Department of Psychiatry, School of Medicine, University of California at San Diego and San Diego Veterans Administration Medical Center, San Diego, CA 92161.

hypophyseal hyperactivity. In this regard, Fang et al. (1981), comparing pre- and post-dexamethasone plasma adrenocorticotropic hormone (ACTH) concentrations in cortisol-hypersecreting dexamethasone-resistant depressed patients and in normal controls, failed to detect any differences between the two groups in plasma ACTH concentrations, either before or after the standard 1.0 mg dexamethasone suppression test. However, Reus et al. (1980) have recently reported that although dexamethasone-resistant depressed patients did not differ statistically from dexamethasone-sensitive depressed patients in predexamethasone plasma ACTH concentrations, the dexamethasone-resistant depressed patients did have significantly higher post-dexamethasone plasma ACTH concentrations than did the dexamethasone-sensitive patients. Most recently, Kalin et al. (1982) have reported that dexamethasone-resistant patients have significantly higher pre- and post-dexamethasone plasma ACTH concentrations than do dexamethasone-sensitive patients. Obviously more studies are needed, but, to date, two of three investigations suggest that cortisol hypersecretion and dexamethasone resistance in depressed patients may be accompanied by elevated ACTH plasma concentrations.

Abnormalities in central noradrenergic (Sachar et al. 1980b), serotonergic (Carroll et al. 1979), and cholinergic (Carroll et al. 1979) neurotransmitter functions have all been mechanistically implicated in the pathophysiology of the presumed limbic-hypothalamic-pituitary-adrenal (CRF-ACTH-cortisol) hypersecretion in depression. With respect to central cholinergic mechanisms, substantial evidence from *in vitro* (Bradbury et al. 1975; Edwardson & Bennett 1974) and *in vivo* animal (Endroczi et al. 1963; Suzuki et al. 1964; Otsuka 1966; Naumenko 1968; Krieger & Krieger 1970; Balfour et al. 1975; Suzuki et al. 1975) and human (Cozanitis 1974; Hill & Wynder 1974; Davis & Davis 1980; Janowsky et al. 1980) investigations suggest that cholinergic agonists may activate the hypothalamic-hypophyseal-adrenal axis to increase cortisol secretion. In addition, Carroll et al. (1979) have demonstrated that dexamethasone resistance can be induced in normal subjects by infusions of physostigmine, an acetylcholinesterase inhibitor with both nicotinic and muscarinic properties. That cholinergic mechanisms might be significantly implicated was suggested by the fact that pretreatment of the subjects with atropine abolished this response. Also administration of ipecac, a potent stimulator of nausea and vomiting, failed to induce dexamethasone resistance, suggesting that this effect may not simply reflect "nonspecific stress."

If central cholinergic mechanisms are involved in the pathophysiology of cortisol hypersecretion in depression, and if the observed elevated plasma cortisol concentrations reflect on increased hypophyseal secretion of ACTH, then it might be hypothesized that plasma beta-endorphin concentrations might also be elevated. In fact, we have recently demonstrated that ACTH and beta-endorphin are co-released in humans under conditions of central cholinergic stimulation (Risch et al., in press). These results parallel the original observations of Guillemin et al. (1977) and others (Pellefier et al., 1977; Rossier et al. 1977) in animal stress paradigms.

An abnormality in acetylcholine neurotransmitter function has also been implicated in depression. Janowsky et al. (1972) have hypothesized that acetylcholine may play an important role in the pathophysiology of affective disorders, and more recently have demonstrated that affective disorder patients are both behaviorally and neuroendocrinologically supersensitive to the effects of physostigmine when compared with nonaffective disorder patients (Janowsky et al. 1980; Risch et al. 1981). Also, Sitaram et al. (1980) have suggested that affective disorder patients may be supersensitive to central cholinergic induction of rapid-eye-movement (REM) sleep, possibly reflecting a generalized cholinergic receptor supersensitivity in depression. Thus a cholinergically regulated hypothalamic-hypophyseal ACTH-beta-endorphin axis might also be cholinergically supersensitive in affective disorder patients.

Method

These studies were conducted under the Food and Drug Administration's approved Investigational New Drug application and with local human subjects committee approval. All subjects gave written informed consent. All subjects were

male and there was no significant difference in age composition among experimental and control groups. To be included, subjects had to be off medication for at least 2 weeks prior to participating in the studies. All subjects received a Research Diagnostic Criteria (RDC) diagnosis based on a Schedule of Affective Disorder and Schizophrenia interview by an experienced diagnostician and collateral information obtained from previous hospitalizations, medical records, and interviews with family members.

Plasma samples for basal morning plasma beta-endorphin immunoreactivty concentrations in the subject groups were obtained as follows. On two separate days, varying between 3 and 7 days apart, an 18-gauge heparin lock catheter was inserted at 8 a.m. in a forearm vein for subsequent plasma sampling. After an accommodation period of 30 minutes, three plasma samples were drawn at 15-minute intervals for subsequent beta-endorphin determinations. The beta-endorphin values from these six samples were averaged to give a mean morning plasma beta-endorphin concentration for each subject.

Differences in cholinergically stimulated hypothalamic-pitutary plasma beta-endorphin concentrations among individuals were determined as follows. After an 8 a.m. insertion of an indwelling heparin-lock venous catheter and subsequent plasma samplings as described above, each subject received methscopolamine 1.0 mg intramuscularly 20 minutes prior to physostigmine or placebo infusions to induce partial peripheral cholinergic blockage. Each individual received infusions of physotigmine salicylate (22 μg/kg) and placebo (sterile saline), 100 cc infused over 10 minutes, in a randomized, double-blind, counter balanced paradigm. Physostigmine and placebo infusions were separated by 3 to 7 days. Plasma samples were obtained from the indwelling venous heparin lock catheters at 10, 20, 30, 45, and 60 minutes subsequent to the physostigmine and placebo infusions. The average of the three baseline pre-infusion plasma beta-endorphin concentrations was subtracted from peak post-infusion plasma beta-endorphin concentrations, to determine each individual's physostigmine and placebo associated increase in plasma beta-endorphin immunoreactivity concentrations.

Four subject groups were compared with respect to: 1) basal morning plasma beta-endorphin concentrations and 2) cholinergically stimulated hypothalamic-hypophyseal plasma beta-endorphin increases. The composition of the groups was SADS/RDC: normals, $N=12$; major depressive disorder (unipolar 6, bipolar 6), $N=12$; nonaffective disorder psychiatric patients, $N=6$; and schizoaffective disorder, depressed, $N=4$.

Significance of changes in plasma beta-endorphin immunoreactivity was determined by repeated measures analysis of variance. Significance of differences among groups in basal plasma beta-endorphin immunoreactivity concentrations and in cholinergically stimulated plasma beta-endorphin immunoreactivity concentrations were determined by one-way analysis of variance and subsequent Scheffé's S Method analysis to compare specific groups.

Plasma beta-endorphin concentrations were measured by radioimmunoassay as previously reported (Risch et al. 1980). The antibody for beta-endorphin has a 50 percent cross-reactivity with beta-lipotropin but less than 0.1 percent with alpha-endorphin and alpha-melanocyte-stimulating hormone, and less than 0.004 percent with leucine and methionine enkephalin. Within assay variability for beta-endorphin is approximately 5 percent and between assay variability is approximately 9 percent. Sensitivity varies from 25-50 pg/ml.

Results

Morning basal plasma beta-endorphin immunoreactivity concentrations were significantly elevated in patients with major depressive illness (123 ± 9.5 pg/ml) and schizoaffective disorder, depressed (131 ± 11.3 pg/ml) as compared with normal subjects (65 ± 6.6 pg/ml) and patients without major affective illnesses (61 ± 4.6 pg/ml): $F(3,30) = 16.2$; $p < 0.0001$ (*see* Figure 1). There was no statistically significant difference in basal plasma beta-endorphin immunoreactivity concentrations between patients with major depressive illness and schizoaffective illness, depressed.

In each group, physostigmine infusions resulted in significant increases in plasma beta-endorphin immunoreactivity concentrations as compared to placebo infusion, in agreement with similar results previously reported (Risch et al. 1980). Physostigmine associated increases in plasma beta-endor-

phin immunoreactivity concentrations were significantly higher in patients with major depressive illness (143 ± 19.4 pg/ml) and schizoaffective disorder (287 ± 51 pg/ml) as compared with normal subjects (73 ± 21 pg/ml) or psychiatric patients without affective illnesses (57 ± 25 pg/ml): F (3,30) = 10.5; $p < 0.0001$ (*see* Figure 2). Physostigmine associated increases in plasma beta-endorphin immunoreactivity concentrations were significantly higher in the schizoaffective group than in the major depressive disorder group, $p < 0.01$, (Scheffé's "S" A Posteriori Method).

Discussion

These findings represent the first report suggesting that plasma concentrations of beta-endorphin, like ACTH and cortisol, may be elevated in depressed subjects, possibly reflective of limbic-hypothalamic-hypophyseal hyperactivity. These results parallel the observation of Terenius et al. (1977) of elevated cerebrospinal fluid "Fraction I" endorphins in severely depressed patients, although presumably cerebrospinal fluid endorphins derived from arcuate nucleus projections to the third ventricle, while the plasma endorphins observed in this study originate from the anterior pituitary. The significance of elevated plasma beta-endorphin concentrations in depressed subjects is unclear. The elevated beta-endorphin concentrations could conceivably be of mechanistic significance in the etiology of the depressed state, or might result as a consequence of the depressed state. Further experimental studies will be necessary to discern the role of elevated plasma endorphin concentrations in depression.

These differences in basal plasma beta-endorphin concentrations among the different nosological groups confound the interpretation of the observed differences in physostigmine asssociated plasma beta-endorphin increases in these same groups. However, the observed enhanced responsivity of the depressed patients, as measured by absolute change scores, is at least consistent with the

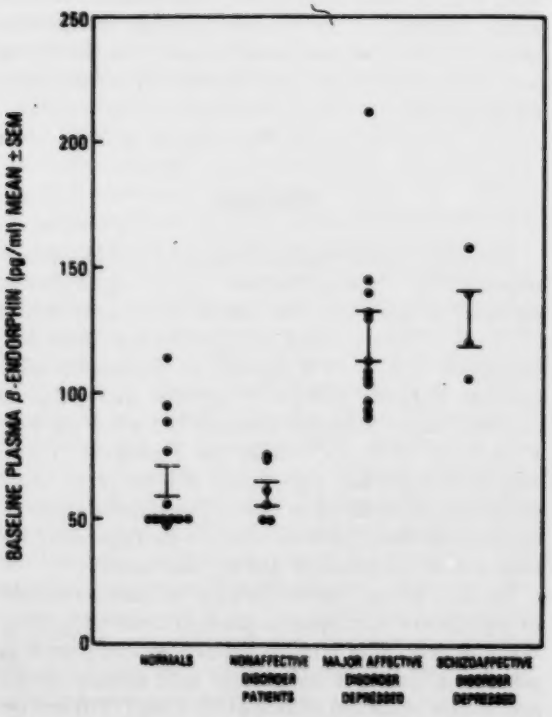

FIGURE 1

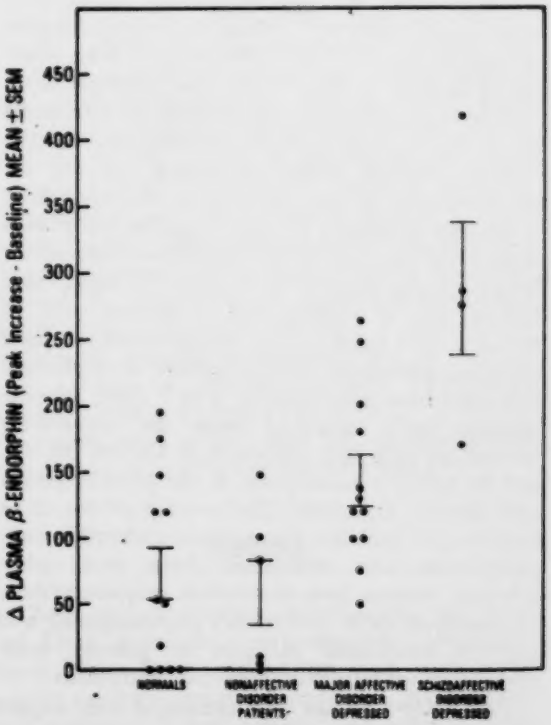

FIGURE 2

possibility of a hypersensitivity of the hypothalamic-hypophyseal beta-endorphin axis to central cholinergic stimulation in depressed patients. These findings add further support for the possibility of cholinergic supersensitivity in affective disorders (Janowsky et al. 1973, 1980; Risch et al. 1981) and parallel the findings of Sitaram and coworkers (1980) of apparent supersensitivity of affective disorder patients to central cholinergic induction of REM sleep. These findings are consistent with the possibility, as suggested by Carroll and colleagues (1979), that central cholinergic hyperactivity could be of mechanistic significance in the elevated plasma concentrations of ACTH and cortisol (and beta-endorphin in this study) observed in depressed patients.

Finally, if the elevated plasma beta-endorphin concentrations and the enhanced release of beta-endorphin in response to physostigmine are specific for depressed patients, beta-endorphin could represent a potential biological state or trait marker for depression.

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Endorphins May Be Involved in the Behavioral Response to Dextro-Amphetamine[1]

Uriel Halbreich, M.D.,[2] Susanna Goldstein, M.D.,[2] Ee-Sing Lo, Ph.D.,[3] and Jean Endicott, Ph.D.[4]

Halbreich et al. (1981a), reported that normal postmenopausal women had a dysphoric response to intravenously administered 0.15 mg/kg dextroamphetamine—a dose that usually causes elation and increased activity in normal young men. This finding has been confirmed by the investigators in a second group of subjects, and may provide a model for the study of the mechanism of the mood and behavioral responses to amphetamine.

Both normal postmenopausal women and normal young men have an increase in plasma levels of cortisol in response to the drug (Halbreich et al. 1981b). Postmenopausal women have a blunted growth hormone response (Halbreich et al. 1980) and they do not show an increase of plasma levels of prolactin (PRL) in response to amphetamine, while PRL levels of young men are increased in response to the same stimulus (Halbreich et al. 1981c). The hormonal responses were also confirmed in the second group of subjects.

Even though some correlations were reported between the baseline levels or the magnitude of change in levels of these hormones, and the behavioral response to amphetamine (Halbreich et al. 1981d; Nurnberger et al. 1981), the authors believe that these do not shed much light on the mechanism of the behavioral response to the drug. Some other mechanisms, compatible with previous findings, should be tested.

It has been proposed (Byck 1976; Belluzzi & Stein 1979) that an excess of endorphins may be involved in euphoria, mania, and amphetamine-induced psychostimulation. There were some suggestions, including that of Gerner et al.

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[2]Department of Psychiatry, Albert Einstein College of Medicine, Bronx, NY 10461.

[3]Center for Neurosciences, Ward's Island, NY 10035.

[4]New York State Psychiatric Institute, New York, NY 10032.

Table

Interaction of Naloxone with Amphetamine Animal Studies

Study	Subjects	Measurement	Antagonism	Dose of Naloxone mg/kg	Dose of d-amphetamine mg/kg
Holtzman (1974)	rats	1) Locomotor activity	Yes	3, 10, 30	0.1, 0.3, 1, 3, 10
		2) Avoidance responding	Yes	10, 30	0.1, 0.3, 1, 3, 10
Holtzman (1974)	mice	Hyperactivity	No	10, 30, 100	1, 3, 10, 30, 100
Dettmar et al. (1978)	rats	Rotation following unilateral lesions of the substantia nigra	a) Yes	0.3, 3	2
			b) No	10, 30	2
Dettmar et al. (1978)	mice	Locomotor activity	Yes	0.3, 1, 3	2
Haber et al. (1978)	rats	Rearing activity	Yes	10	1.5
Haber et al. (1978)	rats	Hyperactivity	No	10	1.5
Horita & Carino (1978)	rabbits	Analeptic effect	Yes	2	0.5
Segal et al. (1979)	rats	1) Locomotor activity	Yes	0.5, 5, 10	0.5, 2.5
		2) Stereotypy	No	Up to 20	2.5
Rethy et al. (1971)	mice	Locomotor activity	No	10	1 - 10
Perez-Cruet et al. (1979)	rats	1) Locomotor activity	Yes	10	0.5, 2.5
		2) Stereotypy	No	10	0.5, 2.5
Adams et al. (1981)	rats	1) Locomotor activity	Yes	1, 2, 4	2.5 (5, 10)
		2) Stereotypy	No (Potentiated)	1, 2, 4	2.5 (5, 10)

(1980), that levels of endorphins may be lower than normal in depression.

These assumptions are far from being established and, at best, they are too simplistic. However, at least in the case of amphetamine, there is some evidence that opioid mechanisms may be involved or may even modulate the behavioral response to the drug. Several groups (those listed in the Table, and a review by Sawynok et al. 1979) reported that the administration of the opioid antagonist naloxone abolished behavioral response to amphetamine in animals. It seems that this interaction is dose-dependent and probably also species-dependent. This is mainly suggested in view of reports from laboratories where different species were tested with different doses (Dettmar et al. 1978; Holtzman 1975). Furthermore, when naloxone was added to amphetamine, the dose-response curve of the later drug was shifted downward and not to the right as would be expected by a direct competition phenomenon. The downward shift may be the common endpoint achieved through a diversity of mechanisms, because other drugs can alter the dose-response curve of amphetamine for operant behavior and locomotor activity in a manner similar to naloxone (Reviews: Weiss & Laties 1969; Rech & Stolk 1970) but naloxone is unique in that it has no influence on these activities when administered alone.

The involvement of opioid mechanisms with human behavioral response to amphetamine is unclear. It was reported by Cohen et al. (1981) that plasma levels of β-endorphin were increased following infusion of 0.3 mg/kg dextroamphetamine to eight normal monozygotic twins. The increase in levels of β-endorphin was significantly correlated ($r = 0.76$) to the increase in levels of cortisol. However, when amphetamine was administered to schizophrenic patients (Schulz et al. 1981), no increase in levels of β-endorphin was found. This finding, which confirmes previous reports concerning cortisol (Halbreich et al. 1981b), may point to an exclusion of β-endorphin as the opioid involved in the behavioral and mood response to amphetamine. Future studies should probably concentrate on other opioids, like met-enkephalin (Belluzzi & Stein 1977). Such studies

should be facilitated once some technical obstacles in the radioimmunoassay of plasma methionine-enkephalin are overcome.

Endorphins also probably interact with, or modulate neurotransmitters and trace amines like phenylethylamine (PEA), whose involvement in the mechanisms of behavioral response to amphetamine has been strongly suggested by several groups (Reviews: Mosnaim & Wolf 1978).

PEA is a naturally occurring amine that mimics amphetamine in its behavioral effects. Amphetamine has been shown to markedly affect PEA levels in the central nervous system. In rabbits it reduces three times the brain content of PEA in the first 30 minutes. In mice and rats it has been shown to increase the turnover of PEA in the brain, markedly augment its synthesis, and accelerate its disposition. Depletion of brain PEA by pretreatment with α-methyldopahydrazine (AMDH) decreases many of the central actions of amphetamine. The time course of changes in stereotype and motor activity of untreated rats in response to PEA also is similar to that of amphetamine.

The role of PEA in the behavioral response to amphetamine has never been adequately demonstrated in humans. In any case, a multivariate approach should be applied to the study of the physiology of the behavioral and mood responses to amphetamine. In future studies an attempt should be made to integrate the various changes in many substances into a comprehensive picture.

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Where Is the "Lesion" in Patients Who Fail to Suppress Plasma Cortisol Concentrations with Dexamethasone?[1]

Ned H. Kalin, M.D.,[2] Stephen J. Weller, M.D.,[2] William T. McKinney, M.D.,[2] Gary W. Kraemer, M.D.,[2] and Steven E. Shelton[2]

Introduction

The failure to suppress plasma cortisol concentrations after the low-dose dexamethasone suppression test (DST) occurs in up to 50 percent of patients with depressive illness (Brown et al. 1979; Carroll et al. 1981; Sachar et al. 1980; Schlesser et al. 1980). This endocrine abnormality has been studied extensively in psychiatric patients but little is known about its underlying pathophysiology. Using depressed subjects and nonhuman primates, the authors have begun to explore the factors mediating this dysfunction. The following studies were designed to further characterize the role pituitary adrenocorticotropic hormone (ACTH) secretion plays in mediating cortisol nonsuppression in depressed patients.

[1]This research was supported by the Veterans Administration.

[2]Psychiatry Service, William S. Middleton Memorial Veterans Administration Hospital and the Department of Psychiatry, University of Wisconsin School of Medicine, Madison, WI 53705.

Address correspondence to: Ned H. Kalin, M.D., William S. Middleton Memorial VAH 2500 Overlook Terrace, Madison, WI 53705.

Materials and Method

Human Studies

Twenty-eight male inpatients, selected for clinical reasons to undergo a DST, were tested by the method of Carroll et al. (1981) within the first week of admission. An 8 a.m. baseline blood sample was drawn, and at 11 p.m. 1 mg of dexamethasone was administered orally. Blood samples were obtained at 8 a.m. and 4 p.m. the following day. Diagnostic and Statistical Manual-III (DSM-III) diagnoses were made from both patient interviews and chart reviews. Data from the human studies will be presented in greater detail in another report (Kalin et al., in press).

Patients were excluded from the study if they suffered from a life-threatening medical illness, poorly controlled diabetes mellitus, alcohol withdrawal, or disease involving the hypothalamic-pituitary-adrenal (HPA) system. Patients taking medications known to interfere with the DST (Kalin et al. 1981) were also excluded. Any patient with a postdexamethasone value of >5 μg/dl in either the 8 a.m. or 4 p.m. sample was considered a cortisol nonsuppressor.

Monkey Studies

The rhesus monkeys used in this study were housed in three peer groups, $N=4$, $N=4$, and $N=3$, and underwent repetitive peer separations as described by McKinney et al. (1972). At the end of the separation week a DST was performed on each animal. Blood was drawn by femoral venipuncture at 9 a.m. on the day before and after the 11 p.m. intramuscular administration of dexamethasone sodium phosphate (150 μg/kg).

Blood Collection and RIAs

All blood samples were collected into glass tubes containing 10.5 mg of EDTA and were immediately placed on ice. The samples were then centrifuged for 10 minutes at 3,000 r.p.m. for the separation of plasma; plasma was frozen at -70°C until assayed.

In the human samples, plasma cortisol concentrations were assayed using an RIA kit supplied by Clinical Assays with a sensitivity of 2 μg/dl.

The monkey samples were measured with a kit supplied by New England Nuclear with a sensitivity of 1 μg/dl.

ACTH immunoreactivity was assayed using an RIA kit obtained from Immunonuclear Corp. (Risch et al., in press) with a sensitivity of 37.5 pg/ml, and intraassay variability of ± 10 percent. Samples from human and monkey experiments were assayed separately in one run.

Results

Human ACTH Concentrations

The patients were separated into two groups on the basis of their cortisol response. The suppressors ($N = 17$) consisted of nine patients meeting criteria for major depressive episode and eight patients meeting criteria for other DSM-III diagnoses. The nonsuppressors ($N = 11$) all met criteria for either major depressive episode or bipolar depression. The Table demonstrates that the mean plasma ACTH concentration in the nonsuppressor group was significantly higher than in the suppressors both before and after dexamethasone administration. In the 8 a.m. predexamethasone samples the nonsuppressors' mean ACTH concentration was 93.9 ± 26.16 pg/ml compared to 51.1 ± 6.47 pg/ml in the suppressors ($t = 1.91$, $p < 0.05$, one-tailed t-test). The 8 a.m. postdexamethasone mean ACTH concentration was also significantly greater in nonsuppressors, 83.9 ± 25.80 pg/ml compared to the suppressors' 45.5 ± 5.20 ($t = 1.79$, $p < 0.05$, one-tailed t-test).

Table

Mean Plasma ACTH (pg/ml ± S.E.M.)

	Suppressors ($N = 17$)	Nonsuppressors ($N = 11$)	One-Tailed t-Test
8 a.m.			$t = 1.91$
Predexamethasone	51.1 ± 6.47*	93.9 ± 26.16**	$p < 0.05$
8 a.m.			$t = 1.79$
Postdexamethasone	45.5 ± 5.20	83.9 ± 25.80	$p < 0.05$
4 p.m.			$t = 1.06$
Postdexamethasone	58.4 ± 5.85	76.9 ± 20.05	N.S.

* 8/17 of the suppressors were < 37.5 pg/ml
** 3/11 of the nonsuppressors were < 37.5 pg/ml

Monkey ACTH Concentrations

The Figure demonstrates the ACTH and cortisol concentrations for the 11 rhesus monkeys at the end of their separation week. In the monkeys cortisol nonsuppression was defined as a 9 a.m. postdexamethasone concentration of > 10 μg/dl. Baseline ACTH concentrations were greater in the monkey cortisol nonsuppressors compared to the suppressors. However, this difference did not reach statistical significance. Postdexamethasone ACTH concentrations were similar in cortisol suppressors and nonsuppressors, but the postdexamethasone cortisol concentrations varied significantly.

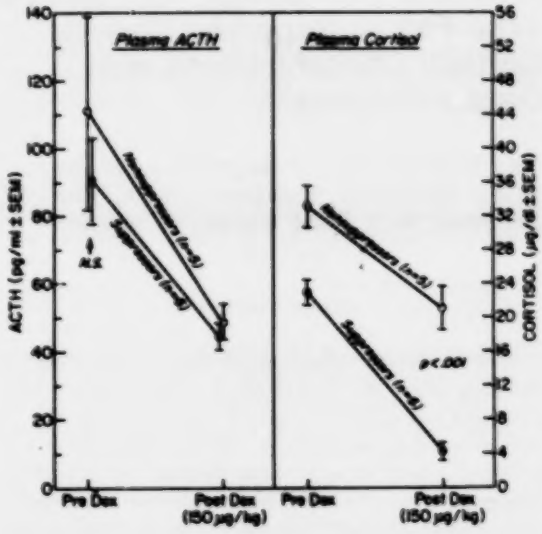

FIGURE. The mean plasma ACTH and cortisol concentrations for 11 rhesus monkeys after peer separation. Cortisol nonsuppression was defined as a postdexamethasone concentration of > 10 μg/dl.

Discussion

Since it has been demonstrated that changing plasma cortisol concentrations are not always directly related to pituitary ACTH secretion (Krieger & Allen 1975; Holaday et al. 1977; Risch et al. in press), it cannot be assumed that the cortisol abnormalities seen in depressed patients reflect hypothalamic and/or pituitary dysfunction.

The authors found that plasma ACTH concentrations are significantly greater in human cortisol nonsuppressors than in suppressors at 8 a.m. before and after dexamethasone administration. The actual differences between the two groups may be even greater than our data show, since 3/11 of the nonsuppressors and 8/17 of the suppressors had predexamethasone ACTH concentrations below the sensitivity of our RIA. In monkeys, baseline ACTH concentrations also tended to be greater in the cortisol nonsuppressors, but postdexamethasone ACTH concentrations did not vary between the suppressors and nonsuppressors as in humans. The similarity in the baseline ACTH concentrations between monkeys and humans supports our earlier suggestion that the rhesus monkey is a reasonable model to use in exploring the regulatory mechanisms of the hypothalamic-pituitary-adrenal system in humans (Kalin et al. 1981).

ACTH concentrations in depressed subjects have been reported in only two other studies. Fang et al. (1981) found essentially no differences among 8 a.m. predexamethasone ACTH concentrations in normals, depressed cortisol suppressors, and depressed nonsuppressors. They also found no differences at 8 a.m. after dexamethasone; however, ACTH concentrations were significantly greater in their nonsuppressor group at 4 p.m. postdexamethasone.

In a preliminary report Reus et al. (1982) found significantly greater ACTH concentrations after dexamethasone administration in depressed cortisol nonsuppressors compared to depressed suppressors. They also reported a trend for higher predexamethasone 8 a.m. ACTH concentrations in the nonsuppressors compared to the suppressors. The Reus et al. study (1982), as well as the authors' findings, support the hypothesis that the failure to suppress plasma cortisol concentrations after dexamethasone is related to increased pituitary ACTH secretion.

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The Epidemiology of Mental Disorders: Results from the Epidemiologic Catchment Area Study (ECA)

Chair: Myrna M. Weissman, Ph.D.
Department of Psychiatry
Yale University School of Medicine
New Haven, Connecticut

An Epidemiologic Perspective on Senile Dementia— Facts and Fragments

Jacob A. Brody, M.D.,[1] and Lon R. White, M.D., M.P.H.[1]

In 1978 there were 2.5 million Americans 85 years and older. By the year 2000 there will be between 3.3 and 6.7 million people 85 and older in this country, depending upon mortality trends. In this age group the estimated prevalence of dementia exceeds 20 percent. The tragedy and the staggering burden represented by this illness and attendant disability is broadly appreciated.

The characteristic pathologic changes of Alzheimer's disease occur in both its senile and presenile forms. Although multi-infarct dementia (MID) accounts for 20 to 40 percent of the dementias of late life, not all patients have either definite MID or the characteristic neuropathologic changes of Alzheimer's disease (Terry 1978). To further confuse matters, these changes are found so frequently among the elderly (dying of all causes) as to raise the question whether senile dementia of the Alzheimer's type (SDAT) is a disease at all or a part of normal aging. Also unclear is the relationship to these conditions of the entity that Kral refers to as benign scenescent forgetfulness (Kral 1978). It can be persuasively argued that pre-senile Alzheimer's disease and SDAT should be considered one disease entity whose vistims range in age from middle to late life. However, a failure to discriminate pre-senile from senile dementia may obscure true differences in pathogenesis if in fact they are not the same disease. The problem of disease definition illustrated by this observation is probably in part responsible for the failure of clear epidemiologic patterns or discernible risk factors to have emerged from previous research efforts.

Although biochemical and anatomic differences between the brains of patients with SDAT and those of patients dying of unrelated conditions have been and continue to be the subject of elegant research efforts, no clear understanding of pathogenesis exists. Epidemiologists have thus far contributed little to the resolution of the problem, since the only factor definitely associated with increased risk is advanced age. Despite this, age-specific incidence and prevalence curves have not been clearly defined. Such definition would contribute to the determination of whether or not SDAT has a unitary pathogenesis, and to the development of measures of frequency for the comparison of individuals grouped according to characteristics or exposures. The methodologic problems most responsible for this paucity of information involve: a) the need to study entire communities of elderly persons, b) the need for a standardized and valid means of classifying individuals according to cognitive ability/disability, and c) for incidence studies, the need for repeated observations over a period of years. These problems are also responsible for uncertainty as to the effect of dementia on life expectancy as it may be modified by the age of onset of the illness.

Prevalence rates for SDAT throughout the

[1]Epidemiology, Demography, and Biometry Program, National Institute on Aging, National Institutes of Health, Bethesda, MD 20205.

world do not vary greatly. Approximately 4 percent of the population over 65 has what can be called a malignant form of senile dementia, with about 20 percent having a mild form of cognitive disability. As mentioned, the prevalence rises sharply with age to approximately 20 percent with severe dementia at age 80 (Mortimer et al. 1981). A general conformity has been noted for data derived from population surveys and to some extent from regional institutional surveys.

Clinicians tend to agree that there are more women than men with SDAT. Electroencephalographic findings over time, however, suggest that fast wave activity is better preserved in females than in males (Busse & Obrist 1963). The female excess may be the result of greater longevity, greater likelihood of seeking medical attention, or greater likelihood of being widowed and living alone, hence requiring institutionalization more frequently than would a male.

Although differences by race have not been reported, confidence in the lack of a difference in dementia incidence between black and white elderly persons is limited because of marked differences in survival. The apparent absence of differences in incidence according to race and sex may be interpreted as suggesting that the pathogenesis of senile dementia may not involve those characteristics and factors known to be associated with differential mortality by sex and race.

Professional pugilists represent the only occupational group which seems to be predisposed to dementia, an observation which has thus far led to no insights into the etiology of SDAT.

A neurologic disease which includes dementia is responsible for approximately 10 percent of adult deaths among the Chamorro people of Guam. Although this syndrome, Parkinsonism-dementia of Gual, shares several neuropathologic characterists with SDAT, its pathogenesis remains as obscure as that of SDAT despite many years of vigorous investigation (Brody et al. 1975). No other geographic or ethnic focus of SDAT is known, except for foci related to familial Alzheimer's disease.

The sporadic form of dementia accounts for the vast majority of SDAT cases. Interest in the familial form relates to the implications of the conclusion that the disease can have a genetic causation (Goudsmit et al. 1981). Thus far these implications have led to no greater understanding of the causes of sporadic SDAT, but have served to guide and encourage avenues of research which consider genetic contributions to pathogenesis. Preliminary findings suggested that familial Alzheimer's disease was transmissible to primates by intracerebral innoculation, and thereby resembled the transmissible spongiform encephalopathies, Kuru and Creutzfeldt-Jacob disease. This appears not to be the case, and the balance of evidence fails to support a slow virus etiology (Goudsmit et al. 1980).

No history of earlier life exposure, rural or urban residence, medical illness, or psychiatric condition appears to predispose to the development of senile dementia. A reported increased risk among persons of lower social status is of uncertain significance, since test batteries used to detect dementia certainly discriminate against such persons and since socioeconomic factors might modify the likelihood that a person would come to medical attention (Gurland 1981).

None of the variables mentioned above has been studied by comparing age-specific prevalence or incidence curves. Instead, most were analyzed by examining age adjusted rates or by comparing the frequency of the variable among SDAT patients with that in the general population or in a control group. Nevertheless, the absence of obvious clustering or of clear differences in risk according to these several factors argues against specific exposures (such as to zoonotic agents or aluminum in antacids) as important etiologic factors.

Although epidemiologic studies have unearthed no patterns of disease occurrence which point to definitive pathogeneses, there are two fascinating, not yet fully substantiated, observations. The first is an association with increased familial frequency of Down's syndrome. This observation is made more exciting by the report that the neuropathologic changes of Alzheimer's disease apparently occur in all (or nearly all) Down's syndrome patients who live to be 40 (Heston & Mastri 1977). The second and less well substantiated observation is of advanced maternal age at the time of birth of individuals who eventually develop SDAT (Cohen & Eisdorfer 1981). It appears that this association may hold for some but not for all groups of SDAT patients, since it was not substantiated by another study in which birth order was investigated as a possible risk factor (Akesson 1969).

It may be meaningful that the risk of SDAT, a condition occurring much more commonly among the very old, seems so unaffected by factors differentially related to longevity. Perhaps this suggests that we should direct our attention away from the sort of adult characteristics, life style, and exposure factors which seem to be involved in determining who survives to be old-old, and toward genetic, early life, and late life characteristics and exposures. The alternative view is that the failure to define risk factors has been due to aggregation of cases of heterogeneous pathogenesis (but clinical similarity) or that the methods of factor and/or endpoint definition have been imprecise or inappropriate.

The epidemiologic data most immediately needed involve the age-specific prevalence, incidence, and clinical course of dementia in medically unselected, longitudinally studied populations of elderly persons. There is also an obvious need for research approaches in which correlations are sought between epidemiologic, neuropsychologic, biochemical, clinical, and pathologic observations. Such studies should reflect the recent burgeoning of information relative to cognitive function evaluation and neurotransmitter metabolism (particularly as related to the cholinergic system), and to hypotheses based on biochemical and neuropathological observations. Careful attention should be give to genetic indicators, including the frequency among family members of other conditions (Down's syndrome, leukemia, immune dyscrasias, or certain neurological diseases), and certain genetic markers (especially HLA markers such as the DB7-CW3 Haplotype, and the HP^1 haptoglobin gene product) (Eisdorfer et al. 1980; Walford & Hudge 1980; Stam & Op den Velde 1978). A different approach would involve the in-depth study of kindreds afflicted with familial Alzheimer's disease or sharing an increased risk for the sporadic form of dementia.

It is essential that, while responding to new knowledge generated by clinical and laboratory studies, the epidemiologist bring to bear on the problem of dementia his most rigorous and imaginative methodologies in the hope of accomplishing: 1) the identification of factors associated with either increased or decreased risk for developing dementia, or 2) the delineation of patterns (i.e., disease occurrence, severity, clinical expression, course) which would point to differentiation of groups of dementia patients having different pathogeneses.

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Workshop—

Antipsychotics and Clinical Response: An Overview

John M. Davis, M.D.,[1] Katherin Hendricks, B.S.,[1] and Javaid I. Javaid, Ph.D.[1]

There have been very few methodologically appropriate investigations of the relationship between antipsychotic drug concentrations in plasma and clinical efficacy. One of the complicating matters is that in chronic schizophrenics who show very little symptomatology (so called "burned-out" schizoprenics) it is often difficult to rate improvement. Curry and Marshall (1968) first noted that there were marked individual differences in plasma levels among schizophrenic patients on comparable doses of chlorpromazine. A range of almost 20-fold difference (approximately 25 to 500 ng/ml) in plasma levels was seen in patients on reasonable clinical doses. A few patients who had very low levels of chlorpromazine failed to show side effects or clinical response. One patient with a high chlorpromazine plasma level showed excessive sedation. When the dose was lowered, plasma levels decreased, and this patient showed a clinical response. It is necessary that these exploratory open studies be verified by properly controlled studies.

Sakalis et al. (1972) treated a small number of schizophrenics and manics with 300 mg of chlorpromazine daily. Since they deliberately included patients who were not acutely ill (because they chose patients amenable to psychophysiological studies), it may have been an inappropriate sample to study for therapeutic effects. Lader (1976) extended the study to include a larger group of new patients, many of whom were acutely ill. However, 300 mg is probably lower than the ED_{50} dose of chlorpromazine (the average dose necessary to produce 50 percent of maximal improvement). For this reason, it would be very unlikely that any patient would have plasma levels above the therapeutic window. The expected relationship between plasma level and clinical efficacy would, therefore, be a linear one at this dose. In a recent report of results on the first 32 patients, the investigators found a correlation of -0.32 between clinical efficacy and plasma levels, which is of borderline significance ($p = 0.4$ level, one-tailed).

Wode-Helgodt et al. (1978) did a methodologically valid study on patients who were treated with randomly assigned fixed doses of 200, 400, or 600 mgs of chlorpromazine per day. In 15 male schizophrenics, there was a positive correlation ($r = 0.82$, $p < 0.01$) between improvement and prolactin elevation at 4 weeks. There was a similar correlation between plasma levels and clinical response. May et al. (1981) studied schizophrenic patients generally treated with chlorpromazine (6.6 mg/kg/day) for 28 days. Plasma chlorpromazine and prolactin levels did not correlate with the clinical outcome.

Chlorpromazine can theoretically be metabolized to 168 different metabolites. It is known that many metabolites of chlorpromazine have pharmacological activity. If a chemical assay measures only the unchanged chlorpromazine, and if the clinical effects are produced to a fair extent by metabolites, and if the amount of metabolite is not well correlated with the amount of unchanged drug, then the presence of active metabolites may obscure the correlation between chlorpromazine-plasma levels and therapeutic efficacy. This may complicate the interpretation of chlorpromazine studies.

Other Antipsychotics

Cotes et al. (1978) treated patients with a fixed dose of flupenthixol and noted a correlation between prolactin levels and total symptom changes ($r = 0.56$, $p < 0.05$).

In 29 schizophrenic patients plasma fluphenazine levels had an inverted U-shaped relationship with clinical response (Dysken et al. 1981). Most nonresponders have either very low fluphenazine levels or very high fluphenazine levels. Also patients treated with haloperidol

[1]Illinois State Psychiatric Institute, Chicago, IL 60612.

showed an inverted U-shaped relationship (unpublished results). Nonresponders have either very low plasma haloperidol or very high haloperidol levels.

Use of Free or RBC Levels

It is the concentration of free drug which is in equilibrium with tissue drug levels. Quantification of free drug is technically impossible at this time, yet potentially quite important. Drugs must cross the blood-brain barrier to reach central receptor sites. These factors of distribution, in addition to rate of metabolism, will determine the amount of drug at receptor site. If some of the mechanisms involved in the drug's distribution across the cell membrane of the red blood cell mimic those governing the passage of drug through the blood brain barrier, then drug levels within RBC (or RBC/plasma ratio) may give additional information. In fact, Manian et al. (1974) have shown similarities between RBC and rat brain synaptosomes-chlorpromazine levels. If the assumption is valid, then RBCs may be a preferred tissue for drug measurement.

Garver et al. (1976) administered butaperazine on a constant dose schedule to acutely symptomatic schizophrenic patients while measuring plasma and RBC levels. Although both plasma and RBC levels vs. response were best characterized by an inverted U-shaped curve, the relationship using RBC levels was more striking. These results support the hypothesis that RBC levels of antipsychotic drugs are a better correlate of clinical response and side effects than plasma levels. These results have been replicated in a completely new sample of patients (Casper et al. 1980).

Blood Levels in Chronic Schizophrenics

Most schizophrenics respond to some degree to neuroleptic drugs and then return home. However, there are occasional patients who show no response to drugs whatsoever and need to be hospitalized in a chronic state hospital. Since some of these very chronic patients are fast metabolizers, failure to respond to drugs might be a possible explanation of their chronicity. Such a chronic population was found to have their plasma and red cell levels substantially below those seen in the acute population (Smith et al. 1979). A similar, very unresponsive group of patients in an acute setting was also studied. Many of these patients had absolutely no clinical response to antipsychotic drugs; many were, indeed, considered for transfer to a chronic facility. In essence, this was the same population as the chronic nonresponders, but identified in an acute setting. These patient also had extremely low plasma and red cell levels. A fair number of these nonresponders did respond when given higher than normal doses of fluphenazine enanthate or decanoate. Since chlorpromazine undergoes first-pass metabolism, an intermuscular formulation may bypass this first-pass effect to achieve an adequate plasma level.

Conclusion

Although all studies do not agree, it appears from the literature that in general, antipsychotics may have a range of drug concentration. Below and above this range the clinical response appears to be less. Measuring blood levels has added an important dimension in treating schizophrenic patients. However, there is a need for more controlled, methodologically valid studies.

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Measurement of Antipsychotics in Patients

Javaid I. Javaid, Ph.D.,[1] Robert D. Linden, M.D.,[1] and John J. Davis, M.D.[1]

It is well established that patients treated with similar doses of antidepressants or antipsychotics have pronounced variations of drug concentrations in plasma (Alexanderson 1972; Forsman et al. 1977; Garver et al. 1977; Hammer & Sjoqvist 1967; Javaid et al. 1981). These interindividual differences have emphasized the need for measuring drug concentrations in blood and correlating these with clinical effects. A number of controlled studies with various antidepressants, have demonstrated a significant relationship between antidepressant concentration in plasma and clinical response. This information, particularly for nortriptyline, imipramine, and lithium, can be used as a guideline for antidepressant concentration in plasma in patients being treated with these medications. The therapeutic or toxic concentrations for most of the antipsychotics, however, have not been established. This scarcity of information has, in part, been due to the lack of specific and sensitive methods for measuring low therapeutic levels of high potency antipsychotics. In recent years, however, there has been emphasis on the development of such methods and at present sensitive and specific methods are becoming available.

In the present studies, drug concentrations in plasma from patients treated with different antipsychotics were measured by gas liquid chromatographic (GLC) methods and radioreceptor assay (RRA). The RRA is based upon the assumption that the therapeutic action of antipsychotic drugs is mediated through their ability to block dopamine receptors. The radiolabeled neuroleptics (such as [^{3}H]-spiroperidol) bound to specific membrane receptors can be displaced by compounds binding to the same receptors. Since RRA measures the total pharmacological activity of the sample *in vitro*, it has great potential for clinical efficacy studies. Potentially, RRA may be used to measure all antipsychotics of different chemical structures in the same assay, expressing the results as "activity units" against one standard (such as chlorpromazine or haloperidol).

Table 1

Neuroleptic Levels by Chemical and Radioreceptor Assays

Drug	N	GLC	RRA	r	RRA Chem
		ng/ml			
Butaperazine	10	152.0	201.0	0.84*	1.3
Haloperidol	20	7.2	10.1	0.62**	1.3
Fluphenazine	20	0.97	7.1	0.85†	7.3
Trifluoperazine	35	0.7	5.7	0.02	8.1

* $p < 0.05$
** $p < 0.01$
† $p < 0.001$

The drug concentrations in plasma from patients treated with four different antipsychotics are shown in Table 1. The parent compounds were used as standards for both the GLC and RRA. The similar values obtained by both methods for butaperazine (RRA/GLC ratio = 1.3) and haloperidol (RRA/GLC ratio = 1.3) suggest that most likely these drugs do not have many active metabolites *in vivo*. On the other hand, RRA values for both fluphenazine and trifluoperazine were 7-8 times greater than the drug concentrations measured by GLC. Higher values by RRA indicate the presence of active

[1]Illinois State Psychiatric Institute, Chicago, IL 60612.

metabolites which were not measured by GLC method.

Since the RRA measures the total inhibitory activity in the sample, theoretically this would be an advantage in clinical efficacy studies, where the investigator is primarily concerned with the clinical effects of the drug, which may be due to the parent drug and/or the active metabolites. It has been shown that *in vitro* potencies of different antipsychotics in blocking dopamine receptors are linearly correlated to their daily doses required for therapeutic treatment in patients (Seeman & Lee 1975). If a certain degree of dopamine blockade is required for the amelioration of schizophrenic symptoms, then the *in vitro* differences of potencies between antipsychotics could account for the differences in clinical doses. Since RRA measures total dopamine blockade activity, one would expect that at therapeutic doses, all antipsychotics would produce similar dopamine blockade activity. However, this was found not to be true. Table 2 shows that the dopamine blockade activity in plasma samples from patients treated with high potency antipsychotics (haloperidol, perphenazine, fluphenazine, and trifluoperazine) was much smaller than butaperazine and thioridazine. Similar results have been reported by other investigators (Calil et al. 1979; Cohen et al. 1980). One possible explanation for large differences in the dopamine receptor blockade activity (as determined by RRA) in plasma from patients treated with different antipsychotics, may be that some of the active metabolites do not cross blood brain barrier. Another possibility is that the binding affinities of different neuroleptics and their metabolites to plasma proteins may vary widely.

Table 2

Neuroleptic Concentrations (CPZ - Equivalence) in Patients Treated with Therapeutic Doses

Drug	Neuroleptic Activity (Chlorpromazine Equivalence)
Thioridazine	1,974
Butaperazine	1,196
Haloperidol	66
Perphenazine	44
Fluphenazine	71
Trifluoperazine	62

The chemical assays (such as GLC) for antipsychotics require sample extraction and are time-consuming; however, they are specific. On the other hand, RRA and radioimmunoassays (RIA) for antipsychotics do not require any extraction, are simple and expedient. These methods, however, are not specific. It has been shown (Rubin et al. 1980) that antibodies prepared against haloperidol by two different methods had different cross reactivities and gave different values of haloperidol in the same samples. Hence, the choice of the method depends upon the specific aims of the investigator, and the methodological details should be kept in mind.

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The *Psychopharmacology Bulletin* is prepared by the Pharmacologic and Somatic Treatments Research Branch of the National Institute of Mental Health. Its purpose is to facilitate the dissemination and exchange of information among the national and international scientific community. The emphasis is on rapid, informal reporting of work which has not appeared in the more formal literature. We invite contributions such as original articles, brief reports, review articles, letters to the Editor, news items, books for review, and announcements appropriate for the *Bulletin*.

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Allen Raskin, Ph.D.
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Psychopharmacology Bulletin
National Institute of Mental Health
5600 Fishers Lane Rm. 10C-14
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We respectfully ask you to adhere to the following guidelines when preparing a paper for the *Psychopharmacology Bulletin*:

1. Manuscript Format: Manuscripts should be typed double-spaced with ample margins, and submitted in triplicate. Do not split paragraphs from one page to another, even if this makes page lengths uneven. Also, do not hyphenate words at the end of a line, even if this makes uneven lines.

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Papers should be written in *third* person, e.g., the investigators found, **Not:** I found, we found. Contents should be *substantive*, not indicative, e.g., the investigator used the gas chromatography method to determine the three molecular structures, **Not:** The author described the method for determining the structure of the drug.

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If a work has two authors, always cite both names every time the reference occurs in the text, e.g., (Swanson & Cole 1974). If more than two authors, cite only the surname of the first author in the text followed by et al., e.g., Williams et al. 1963.

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Use generic names in referring to drugs; trade names may be given in parenthesis the first time a drug is mentioned only.

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Allen Raskin, Ph.D.
Editor-in-Chief

Lillian Altman
Managing Editor

Psychopharmacology Bulletin
National Institute of Mental Health
5600 Fishers Lane Rm 10C-14
Rockville, MD 20857

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Fellowship Program

The University of Texas Health Sciences Center announces the third year of their Clinical Psychopharmacology Fellowship Program for physicians who have completed psychiatric residency training. Two positions are open for the 1983-1984 year. The fellow will be eligible for an appointment as Instructor in the Department of Psychiatry and will receive a commensurate stipend.

The program inclues: a) clinical research experiences in several of the ongoing studies in the department; b) clinical psychopharmacological preceptorial work; c) participation in one of the ongoing studies of biological disturbances in major psychiatric illness; d) wet laboratory experience in analytical methods; e) an integrative tutorial series to provide an overview of neuropharmacology, biological hypotheses of psychiatric disorders, and clinical investigative techniques; f) participation in graduate school and other Health Science Center courses and seminars pertinent to the learning needs of the fellow; and g) opportunity to emphasize study and training in a selected clinical area.

For further information, please contact: Charles L. Bowden, M.D., Nancy U. Karren Professor of Psychiatry, Dept. of Psychiatry, The University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78284.

* * * * *

Meeting Announcements

The 1983 meeting of the **Society of Behavioral Medicine** will be held at the Hyatt Regency in Baltimore, Maryland on March 2-5, 1983. There will be a special track for the Fourth Annual Meeting on the topic of Behavioral Medicine in Industry. For further information, please contact: Thomas J. Coates, Ph.D., Program Chair, Society of Behavioral Medicine, P.O. Box 8530, University Station, Knoxville, TN 37996.

* * * * *

Announcement and call for papers for the VIIth World Congress of the **International College of Psychosomatic Medicine** to be held in Hamburg, Federal Republic of Germany, July 17-22, 1983. This Congress will take place immediately after the World Congress of Psychiatry in Vienna. Topics for the plenary session will be: early identification and prevention of psychosomatic disorders; maintaining health despite stress and adverse circumstances; the effectiveness of psychotherapy on specified psychosomatic disorders; integrational models of psychosomatic pathogenesis; taxonomic subgroups within psychosomatic diseases; the psychosomatic problems involved in somatic treatment; integration of psychosomatics into hospital treatment; and the influence of social change and economic factors on psychosomatic disorders.

Epidemiology, original points of view, theoretical viewpoints, pain, sleep and dreams, hypnosis, behavioral therapy, psychosomatic illness in the elderly, and various other topics will be discussed in the symposia.

For further information, contact Psychosomatics 83, Hamburg Messe und Congress GmbH, Congress Organization, P.O. Box 302360, D-2000 Hamburg 36, Federal Republic of Germany.

* * * * *

The **Canadian College of Neuropsychopharmacology** will be holding its Sixth Annual Scientific Meeting in Saskatoon, Saskatchewan on May 25-28, 1983. The sponsors are various departments of the University of Saskatchewan. The meeting will include an academic lecture by the 1982 Heinz Lehmann award winner, Dr. T. L. Sourkes; plenary lectures; symposia; roundtables; workshops; oral communications; and poster sessions.

For further information, please write to 1983

CCNP Meeting, c/o Psychiatric Research Division, University Hospital, Saskatoon, Saskatchewan S7N OXO, Canada.

* * * * *

The Second International Congress on Drugs and Alcohol will be held December 18-22, 1983 in Tel-Aviv, Israel. This multidisciplinary congress is being organized by the Society for Medicine and Law in Israel and the Israel Medical Association, and will provide an excellent opportunity for researchers, intervention agents, and policymakers to exchange their views, concerns, and future plans.

Those interested should contact: Congress Secretariat, Peltours Ltd., Congress Department, P.O. Box 394, Tel Aviv, 61003 Israel.

Book Reviews

• **The Psychobiology of Affective Disorders,** edited by Joseph Mendels, M.D. and Jay D. Amsterdam, M.D., presents the proceedings of a symposium held in February 1980. The symposium gathered a group of experts to review current knowledge of psychobiologic factors associated with clinical depression. The presentations and discussions focused on biological factors in the etiology of depression and as predictors of differential response to psychopharmacologic treatment.

The 14 papers presented represent a wide range of research efforts and attempt to summarize relevant data on the interaction of specific factors as neurotransmitters, receptors, hormones, and genes with the psychologic and environmental components of depression. The volume expresses an optimistic view that significant progress is being achieved in understanding the psychobiology of affective disorders. Although considerable research is required to fully understand the complexities of this problem, the contributors are encouraged that this psychobiological avenue of investigation has great potential for the development of a rational approach for the diagnosis and therapy of affective disorders.

In the opening chapter, Martin Katz discusses the epidemiology of depression and explanations for its apparent increasing incidence, including increased awareness of its presence. Next, David Dummer presents recent clinical, biologic, and genetic data supporting the subclassification of affective disorders into unipolar, bipolar I, and bipolar II subtypes.

Elliot Gershon's paper reviews the evidence that genetic factors are of importance in determining vulnerability to major affective disorder. The usefulness of information about affective disorders in first-degree relatives for treatment and prevention of these disorders is presented.

Three chapters by James Maas and Yung Huang, Jay Amsterdam and Joseph Mendels, and David Janowsky provide an in-depth review of noradrenergic, serotonergic, and cholinergic neuronal system functioning and depression. Alan Fraser and Joseph Mendels focus on evidence that repeated administration of antidepressant drugs leads to compensatory neuronal processes that modify the initial effects of an enhanced noradrenergic response. Each of these contributions skillfully delineates the currently conceptualized role of these neurotransmitters in the complex regulation of affect and the pathophysiology of affective disorders.

The theoretical and clinical significance of the neuroendocrine aspects of depression is presented by Bernard Carroll. Carroll describes the utility of the dexamethasone suppression test (DST) as a measure of neuroendocrine disinhibition. About 50 percent of endogenously depressed patients show this phenomenon.

In Boyd Hartman's presentation, depression is conceptualized as one component of a dysregulation of general central homeostatic mechanisms. This research indicates that tricyclic antidepressants have pharmacologic effects on cerebral vascular permeability mediated by the central adrenergic regulatory system. Thus, he believes these drugs may have biologically important central effects on non-neuronal tissues.

In two additional chapters, recent pharmacologic and clinical studies and sleep and circadian rhythm disturbance in depression are reviewed by David Hawkins. In the concluding three chapters, George Winokur, Morris Lipton, and Jay Amsterdam and Joe Mendels discuss the advances in clinical psychiatric practice resulting from psychiatric research, and attempt to sum-

marize new psychobiological strategies in affective illness.

This book is valuable as an wide-ranging review of the psychobiology of affective disorders. Generally, the contributions are concise, readable, and informative reviews of past and current work in the area. Several of the authors present provocative new theories and hypotheses. The inclusion of the open discussion following each presentation provides additional perspectives on the topic. The book contains valuable information and extensive references for both clinicians and psychopharmacologic researchers.

The book may be ordered directly from the publisher, S. Karger, Basel, Switzerland. Price: SFr. 39./DM47./U.S. $23.50. 220 pp. soft cover.

Jack Blaine, MD.,
National Institute of Mental Health
Rockville, Maryland

* * * * *

• **The Missing Link,** by Walter J. Garre, is a philosophical and psychological attempt to explain the "transition from animal instinct to the human mind." The main result of this transition, Dr. Garre states, is man's sense of self-glory. All human motivation stems from this need to feel important, resulting in unrealistic rationalizations and beliefs about other humans and nature. Included are the beliefs that man can control nature, that mankind has a specific purpose, and that there is a God who is aware of the existence of each individual.

The one recurring theme in this book is that of strict determinism. Each human being is physically and emotionally the product of his genetic endowment and environmental experiences. Free will is an unrealistic creation to enable the individual to feel special.

Dr. Garre attempts to explain a wide range of topics through his deterministic theory. Some of these topics are evolution, personality disorders, depression, violence, anxiety, sexual disorders, love, and art. Most personality traits, claims Garre, arise as a result of the degree of acceptance and importance felt by the child in early years. The reader is continuously reminded, however, that the parents themselves are only as adequate as their parents prepared them to be.

The Missing Link is a thorough discussion of determinism. It also serves as a primer on Darwinian theory as well as Freudian and Jungian theories of personality. Unfortunately, this book does not provide any insights on the transition from animal instincts to the human mind, as the title claims. It does discuss the differences or lack of differences between humans and animals. The book also does not provide "scientific proof," as the author states, of his theory. Rather, Dr. Garre explains contradictions between determinism and various twin studies by pointing out the inadequacies of the studies cited; he does not provide evidence, scientific or otherwise, to substantiate his beliefs.

Despite its shortcomings, the book does make interesting and, at times, provocative reading.

The book may be ordered directly from Philosophical Library, 200 West 57th Street, New York, NY 10019. Price:$15.00; 293 pp.

Sarah Raskin
Johns Hopkins University
Baltimore, Maryland

• **Compendium of Current Source Materials for Drugs,** compiled by Eutychia Londos, is an annotated bibliography of sources where librarians, health professionals, and interested lay persons can find information on drugs. The 12 sections of this text include the following types of materials: standard reference books for both prescription and nonprescription drugs; dictionaries and encyclopedias; evaluative and comparative sources; sources for laws and regulations, including names and addresses of national and international enforcement agencies; books and pamphlets for general reading, including alcoholism, drug abuse, and drug therapy; directories of education information; treatment centers and agencies, with national information centers for smoking listed; bibliographies on drug sources; journal and newsletters; reports; audiovisual catalogs and indexes, including names and addresses of pharmaceutical companies providing free loan film services; and computers and on-line databases, annotating the most recent developments in this new area of drug information retrieval. A combined author and title index is provided.

The author, Eutychia Londos, is a librarian working primarily with audiovisual materials and computerized literature retrieval services. Updates or supplements to this compendium are planned as new source materials become available.

The book may be ordered directly from the publisher, Scarecrow Press, Inc., 52 Liberty Street, P.O. Box 656, Metuchen, N.J. 08840. Price: U.S. $12.50; 146 pp. Size: 8 1/2 x 11.

Allen Raskin, Ph.D.
National Institute of Mental Health
Rockville, Maryland

New Journal

Clinical Gerontologist, a new journal in the field of aging and mental health, edited by T.L. Brink, Ph.D., is now being published by The Haworth Press, Inc., 28 East 22nd Street, New York, NY 10010. The Journal is written and refereed by and for mental health practitioners. The editor is interested in topics such as organic brain syndrome, depression, paranoia, hypochondriases, psychosomatic disorders, suicide, multidisciplinary teams, alcoholism in later life, and helping families of dependent elders.

New Books

• **The Handbook of Biological Psychiatry.** Edited by Prof. Dr. Herman van Praag, Malcolm Lader, Ole Rafaelsen, and Edward Sachar. Individual titles are: Disciplines Relevant to Biological Psychiatry; Brain Mechanisms and Abnormal Behavior (Psychophysiology); Brain Mechanisms and Abnormal Behavior (Genetics and Neuroendocrinology); Brain Mechanisms and Abnormal Behavior (Chemistry); Drug Treatment in Psychiatry-Psychotropic Drugs; and Practical Applications of Psychotropic Drugs and Other Biological Treatments. The books can be purchased individually or in a set. The entire set price (6 volumes) is $370.75 (Twenty percent higher outside the U.S. and Canada). New York: Marcel Dekker, Inc., 270 Madison Avenue, New York, NY 10016.

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• **The Biology of Anxiety.** Edited by Roy J. Mathew, M.D., D.P.M. Brunner/Mazel Publishers, 19 Union Square, New York, NY 10003. Price: $30.00; 312 pp.

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• **The Substance Abuse Problems.** Sidney Cohen, M.D. (ed.). The Haworth Press, 149 Fifth Avenue, New York, NY 10010. Price: $19.95, softcover; $29.95, hardcover.

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• **Biological Treatments in Psychiatry.** Lothar Kalinowsky, M.D., (ed.). Grune & Stratton, Inc., 111 Fifth Avenue, New York, NY 10003. $49.50.

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Lithium and Manic Depression: A Guide. Written by John Bohn, R.Ph. and James Jefferson, M.D., with assistance from other staff members at the Lithium Information Center, Department of Psychiatry, University of Wisconsin-Madison, 600 Highland Avenue, Madison, WI 53792. Price: $3.00 per copy (1 to 10 copies); $2.00 per copy (more than 10 copies).

Notice

Use of Approved Drugs of Unlabeled Indications*

The appropriateness or the legality of prescribing approved drugs for uses not included in their official labeling is sometimes a cause of concern and confusion among practitioners.

Under the Federal Food, Drug, and Cosmetic (FD&C) Act, a drug approved for marketing may be labeled, promoted, and advertised by the manufacturer only for those uses for which the drug's safety and affectiveness have been established and which FDA has approved. These are commonly referred to as "approved uses." This means that adequate and well-controlled clinical trials have documented these uses, and the results of the trials have been reviewed and approved by FDA.

The FD&C Act does not, however, limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens of patient populations that are not included in approved labeling. Such "unapproved" or, more precisely, "unlabeled" uses may be appropriate and rational in certain circumstances and may, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature.

The term "unapproved uses" is, to some extent, misleading. It includes a variety of situations ranging from unstudied to thoroughly investigated drug uses. Valid new uses for drugs already on the market are often first discovered through serendipitous observations and therapeutic innovations, subsequently confirmed by well-planned and executed clinical investigations. Before such advances can be added to the approved labeling, however, data substantiating the effectiveness of a new use or regimen must be submitted by the manufacturer to FDA for evaluation. This may take time and, without the initiative of the drug manufacturer whose produce is involved, may never occur. For that reason, accepted medical practice often includes drug use that is not reflected in approved drug labeling.

With respect to its role in medical practice, the package insert is informational only. FDA tries to assure that prescription drug information in the package insert accurately and fully reflects that data on safety and effectiveness on which drug approval is based.

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Adverse Drug Reactions

Safe Passage (How Good a Guarantee?)

Paul Leber, M.D.

In the author's first three contributions to this column, he examined aspects of two alleged causal relationships between drug exposure and untoward events (lithium and leukemia; neuroleptics and sudden death), and the more general problem of common untoward clinical events falsely attributed to drug exposure.

In this column, the author will address another class of problem which is frequently encountered in the process of conducting drug safety assessments. What is the significance of failing to detect any untoward events during drug exposure? In other words, what conclusions may be drawn from a report of "safe passage?"

Clearly, safe passage by several persons on a particular voyage does not guarantee that all travelers will be kept out of harm's way on similar trips. Any assurance that can be drawn from reports of safe passage must be qualified by a consideration of how many individuals have attempted the voyage, and the qualities and character of those who enjoyed safe passage.

Consideration of each of these caveats is especially critical when a report of "safe passage" is likely to lead to an increased use of a potentially toxic drug in what may be called a "physiologically disadvantaged" population.

A case in point is a recent and reassuring *New England Journal of Medicine* article on the apparent safe use of two tricyclic antidepressant drugs in ambulatory patients with heart disease (Veith et al. 1982). Before discussing the article and its relationship to safe passage, however, some background on the risks attributed to the use of tricyclics in patients with cardiovascular disease is necessary.

The cardiotoxic effects of large overdoses of tricyclics were recognized by 1959 (Mann et al.). Concern about the danger they may pose to cardiac patients (when used at therapeutic doses) can be traced to 1) a 1961 report of severe postural hypotension and associated myocardial infarctions (Muller et al.), and 2) a 1970 report of an increased incidence of sudden death (Coull et al.). Other evidence about tricyclics in heart disease, however, is more comforting. One widely quoted hospital based epidemiological survey by the Boston Collaborative Drug Surveillance Program (1972), for example, suggests that the short term outcome of hospitalized patients with "cardiovascular disease" was not affected by treatment with tricyclics. The usefulness of this report has been questioned, however. In the view of one of the preeminent groups in the field, the Boston study has many shortcomings and is not as reassuring as it may seem at first reading (Glassman & Bigger 1981). In particular, the study's sanguine outcome must be evaluated in light of the following information: 1) the average dose of tricyclic administered was below 81 mg per day, and 2) the mean observation period was 2 weeks or less for the two largest specific drug groups (amitriptyline and imipramine).

On the other hand, not all the evidence is negative: one of the pharmacologic properties of tricyclic drugs may offer protection to some patients with heart disease. Bigger and Glassman's

Note: This article was written by Dr. Leber in his private capacity. No official support or endorsement by the Food and Drug Administration is intended or should be inferred.

group have documented that the quinidine-like, anti-arrhythmic effect of imipramine may, under selected conditions, prove beneficial to the patient with heart disease (Bigger et al. 1977).

Given this background, the potential significance of the investigation by Veith and his colleagues can be readily understood. Clinicians are often confronted with significantly depressed patients who have serious heart disease. Aside from the dysphoria and suffering associated with the depressed state, depression may interfere with successful physical, social, and vocational rehabilitation of the patient. Thus, a direct examination of the risk of antidepressant drug use in depressed cardiac patients is an important undertaking which commands the interest of the medical community. When the results of such a study support the relative safety of antidepressants, one may anticipate a change in tricyclic use in clinical practice. Indeed, one may expect the influence of the article to be fairly widespread, given the large readership of the *New England Journal of Medicine*. In light of these considerations, it seems important to examine, critically, the message of safe passage conveyed in the article, be it explicitly intended by its authors or not.

The paper is entitled, "Cardiovascular Effects of Tricyclic Antidepressants in Depressed Patients with Chronic Heart Disease." Below the title, set in bold type, is the synopsis of the study which states, in part, "Our findings underscore the need for a reappraisal of the cardiovascular risks of tricyclic antidepressants and suggest that in the absence of severe impairment of myocardial performance, depressed patients with preexisting heart disease can be effectively treated with these agents without an adverse effect on ventricular rhythm or hemodynamic function." It seems possible that a reader may interpret this statement as a more or less unqualified endorsement of tricyclic use in heart disease.

Admittedly, the discussion section of the paper presents a more comprehensive analysis of the study's limitations. The authors note that their patient sample contained relatively few patients with seriously impaired cardiac performance (i.e., ejection fractions below 0.35). They comment that their paper cannot resolve that issue of the relationship between sudden death and tricyclics. Nevertheless, they are fairly sanguine about the safety of tricyclics in "patients considered at high risk for cardiovacular side effects. . ."

How was this conclusion reached in a study involving 17 drug-treated patients? More important, is the conclusion reasonable? A fair response to these questions must begin with a detailed examination of the study.

Twenty-four patients (outpatients?) from the psychiatric and medical services of the Seattle V.A. Medical Center took part in this double-blind, parallel-control design, clinical trial. All subjects were males with heart disease who were catagorized as suffering from "secondary major depressive disorder, endogenous subtype, according to research diagnostic criteria." All participants had scores of 18 or more on the 17-item Hamilton Depression Scale and had been depressed for a mean of 7 months prior to treatment. Twenty-three of the patients had had a previous myocardial infarction (none within 2 months of the study). Although no patients had "evidence of overt congestive heart failure," "many" were taking cardiac medications throughout the trial.

Patients were assigned to one of three treatment groups (imipramine, doxepin, or placebo) for a period of 4 weeks by a "modified randomization" procedure. Subjects were not stratified on measures of ventricular performance. Consequently, although the differences among the group means were not significant (small "n"?), four of the five subjects with the lowest baseline ejection fraction values were distributed to the placebo group. In characterizing the patient sample, it is important to note that only one of the eight imipramine recipients had an ejection fraction at rest of less than 0.40. Indeed, it appears that eight drug-treated patients had ventricular performance, at rest and upon exercise, which fell in the normal range (N.B., "appears" because the individual results can only be estimated by extrapolation from a graph.) Indeed, on average, the sickest patients were assigned to placebo (i.e., the mean duration of baseline exercise was significantly lower in the placebo than in the imipramine group).

Patients on active treatment were begun on 50 mg p.o., h.s., and advanced on an every 3-day fixed schedule to the maximum dose permitted by side effects. A maximum dose limitation of 150 mg that had been imposed initially was removed

because of good experience with the first eight drug-treated patients. Dosage, however, was held constant in the last week of treatment in an attempt to reach steady-state conditions. At the end of week 4, plasma levels of imipramine ranged from 34 to 468 nanograms per ml (mean of 147) and plasma levels of doxepin ranged from 21 to 646 nanograms per ml (mean of 174).

The authors evaluated the patients over the course of the trial on several measures of depression and cardiac function. Put succinctly, the results showed that the drug-treated groups enjoyed a significant within-group improvement from their baseline depression assessments, and a two-way Analysis of Variance (ANOVA) demonstrated a significant (?overall) drug-placebo treatment difference.

The assessments of cardiac function did not reveal any adverse effect of antidepressant treatment. Specifically, there were no statistically significant changes in left ventricular function as measured by a change in the mean ventricular ejection fraction (CVEF) at rest or with exercise.*

Evidence of ventricular irritability based upon the number of premature ventricular contractions per hour was difficult to assess because of the very high within, subject variability observed between repeated observations. Estimates of cardiac electrical activity based upon weekly 12 lead EKG recordings (i.e., heart rate, PR interval, QRS interval, and corrected QT interval) also showed no clinically important differences between the groups.

Finally, recorded blood pressures did not identify a statistically significant change in the extent of orthostatic hypotension observed pre- and post-treatment in the three treatment groups. Nevertheless, it is important to note that postural dizziness associated with documented orthostatic hypotension did occur in one patient given imipramine and in three given doxepin. One patient on doxepin had a syncopal episode.

*Ventricular ejection fraction (VEF) is now widely used as a measure of ventricular performance. The VEF is a dimensionless index, obtained by detecting radiation over the precordium following the intravascular injection of radioactive material. It reflects the average fraction of the end-diastolic volume ejected during systole. It is presumed that the difference between two successive measurements of the ejection fraction (i.e., the change in VEF or CVEF) reflects a change in ventricular performance. Thus, if no change in performance occurs, the CVEF is zero; if performance worsens, the CVEF will be less than zero (i.e., it will be negative).

Returning to the original question posed by this author, given the results of the Veith study, can one reasonably conclude that it is "safe" to use tricyclics in depressed patients with cardiovascular disease?

The answer, of course, depends upon what one is willing to accept as evidence of "safety" for this particular indication and population. Clearly, because "safety" is an abstraction, safety can never be demonstrated directly. Instead, one estimates the risk of injury associated with drug exposure and equates the relative absence of risk with some degree of relative safety. Thus, for practical purposes, the drug safety assessment process is directed at making a reliable estimate of the incidence of untoward events in the population upon drug exposure. Then, based upon some undefined process, personal beliefs about the magnitude of the risk, the benefit of the drug's effect, and the gravity of the condition being treated, are integrated to reach a judgment about the drug's relative safety.

Viewed from this perspective, the value of the Veith study as a predictor of tricyclic safety depends upon the precision of the estimate of the risk of serious injury that can be obtained from its results.

Judged by these standards, the Veith study, involving merely 17 drug-treated patients, can be expected to detect only relatively common risks and to be rather imprecise in estimating the bounds of these risks. This should not be especially surprising, as large multicenter studies involving hundreds of patients are known to be relatively insensitive to untoward events that occur at frequencies below 2 or 3 percent. The limitation that a small sample size places on the ability to detect a significant risk can be illustrated for the sample size used in the Veith study, 17.

To make the argument clear, let us assume that the population actually contains two classes of individuals: 1) those who will and 2) those who will not come to grief if treated with tricyclics. Given this assumption, how large a proportion of the depressed cardiac patient population might be at risk despite the safe passage of the 17 individuals observed in Seattle?

This question can be answered using the binomial distribution as a model. The question is formally stated in the following manner. How large must "p," the proportion of subjects who will suffer harm, be to be 95 percent certain that at

least one patient in a sample of 17 will suffer the event? If no events are observed in the sample of 17 patients, then we can be equally certain that the true proportion, "p," must be less than the one calculated. For the binomial distribution, the probability of detecting one or more events is unity minus the probability of detecting none in a sample of 17 individuals. Setting the probability of the statement at 95 percent, the equation can be solved for the value of "p": $[0.95 = 1-(1-p)^{17}]$. The calculated value of "p" is approximately 0.16. Thus, the failure of Veith and his colleagues to detect even a single instance of tricyclic-induced ventricular impairment among 17 patients can only be considerec unlikely if more than 16 percent of the depressed cardiac population were going to suffer a serious impairment of ventricular performance when treated with tricyclics. This is not a very reassuring result regardless of one's vantage point.

If 17 counts of safe passage offer little reassurance, what can account for the Seattle groups' belief that the outcome of their study "underscore(s) the need for a reappraisal of the cardiovascular risks of tricyclic antidepressants. . .?"

The problem may lie in the deceptive appeal of average change scores with values close to zero. Indeed, a change score measurement close to zero conveys virtually the same information as a report of safe passage. Unfortunately, such scores may lend themselves to overinterpretation.

To illustrate the point, consider the change in baseline ventricular ejection fraction (CVEF) associated with tricyclic use. As mentioned earlier, if tricyclics have no effect on the ventricular performance, the mean value of the CVEF (VEF on drug-VEF baseline) in the population of depressed patients with heart disease will be zero. Of course, it will not be zero for every patient. In fact, for purposes of assessing safety, the variability of the CVEF is as important a measure as the mean itself. Specifically, even if the mean is zero, a substantial proportion of patients might still be at considerable risk if variability in the population is great. Thus, the assurance given by Veith and associates that their study had an 84 percent chance to detect a change of 10 percent in the mean VEF (i.e., a negative CVEF equal or greater than one-tenth of the baseline VEF) is not as comforting as it appears at first reading. This is because we are not so much interested in the mean value of the CVEF (as it is essentially zero) as we are in the relative proportion of the population that will have clinically important CVEF values (i.e., ones with larger negative values).

A more appropriate goal of a safety assessment, therefore, is to construct statistical tolerance limits for the CVEF. Because we are only interested in decrements in ventricular performance, we wish to find one-sided limits. Specifically, we wish to find a value, A, above which at least a proportion P, of the population will lie (Natrella 1963).

Tables for calculating such limits exist. Using resting CVEF data for the nine sickest drug-treated patients (mean CVEF was 0.01; sample standard deviation reported as 0.03) the following may be stated with a 90 percent confidence: assuming normality, at least 90 percent of the distribution will have a CVEF greater than a value equal to the sample mean minus the product of the tabled value of K (2.133 for a sample size of nine) and the sample standard deviation. [Lower limit of CVEF = $0.01-(2.133 \times 0.03) = -.054$]. (*See* Table A-7 in Natrella 1963.) In other words, 10 percent of the population can reasonably be expected to have a 0.05 or greater fall in their VEF at rest when treated with tricyclics. Even this estimate, however, may be too optimistic. The tolerance limit calculations are based upon the assumption that the patient sample is a random one from the population (i.e., that it is representative) and upon the assumption that CVEF scores follow a normal distribution. Neither of these assumptions need be correct.

Assuming, however, that the tolerance limits are reasonably accurate, how clinically significant will a fall of 0.05 units in resting VEF be for 10 percent of depressed patients with serious heart disease? Obviously, there is no ready answer. It does seem reasonable, however, that a fall of this sort is more likely to be important to the patient with marginal cardiac reserves than it is to the typical patient in the Seattle study who had VEFs in the normal range.

These calculations have been presented to illustrate the limits of safe passage arguments. From the perspective of the public health, 17 patients is very few indeed. It is of interest to this author that Veith and his associates recognized the problem when they noted that their results

could not provide an estimate of the risk of sudden death. They clearly recognized that failure to detect an event in a small number of subjects is not especially reassuring. However, when Veith and his colleages were able to measure a variable, they behaved as though they had additional information which permitted them to make stronger inferences about safety than they might had they interpreted their experience as 17 counts of safe passage. In this author's view, it is more appropriate (i.e., conservative) to treat the measurements of cardiovascular performance as merely "hard data" corroboration (i.e., an independent check) of each count of safe passage.

Viewed in this light, the more or less uneventful passage of 17 mildly ill cardiac patients would not justify a reappraisal of the risks of tricyclic drugs. Indeed, syncope, a major recognized risk of tricyclic treatment for the patient with cardiovascular disease, did occur. Incidentally, this clinically significant event would not have been identified by examining the mean values for increments in orthostatic hypotension observed in each drug-treated group.

Before ending the column, this author wants to emphasize that his concern is not with the work nor with the results of the investigative team that conducted this very well-designed and interesting clinical trial. We will all be well served if the work in Seattle is continued, and if other studies, of similar design, are conducted. This author's concern is with the relatively strong implication of relative safety presented by the paper, especially in its lead abstract. While the author hopes that the implication is warranted, he fears that it may not be. Until larger samples of more severely ill cardiac patients are studied, wisdom suggests that tricyclics be used with caution in patients with compromised cardiovascular function.

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Brief Reports—

Supersensitivity, Drug Withdrawal, and Open Field Behavior

João Palermo-Neto, M.S., Ph.D.[1]

The open field has been used to study withdrawal from long-term drug treatment (Bernardi & Palermo-Neto 1979; Bernardi et al. 1981; Capaz et al. 1981; De Lima & Palermo-Neto 1980; Palermo-Neto & De Lima, in press). Thus, abrupt withdrawal from long-term haloperidol administration in increasing doses enhanced general activity of rats in an open field (Bernardi & Palermo-Neto 1979). Identical findings were observed after withdrawal from long-term treatment with diphenylhydantoin (De Lima & Palermo-Neto 1980), ethanol (Capaz et al. 1981), and sodium barbital (Palermo-Neto & De Lima 1982). The open field was also used to compare the effects of single and long-term haloperidol administration (Bernardi et al. 1981). The effects of withdrawal from the neuroleptics were explained by a development of supersensitivity in the central dopaminergic receptors. Indeed, a significant displacement to the left of the dose-response curve for apomorphine-induced stereotypy in rats on abrupt haloperidol withdrawal was observed (Bernardi et al. 1981). Central nervous system (CNS) supersensitivity was also used to explain withdrawal effects for the remaining drugs employed. Thus, in ethanol-withdrawn mice a positive correlation was found between locomotion plus rearing frequencies and audiogenic-induced seizure susceptibility (Capaz et al. 1981). Equal results were detected after withdrawal from long-term diphenylhydantoin (De Lima & Palermo-Neto 1981) and sodium barbital (Palermo-Neto & De Lima 1982). In these latter two studies, drug removal also made rats more sensitive to convulsions elicited by maximal transcorneal electroshock.

There is a close relation between CNS supersensitive phenomena and the "withdrawal syndrome" observed after withdrawal from long-term administration of CNS-depressant drugs (Collier 1966, 1968; Sharpless 1964, 1969, 1975). In rats, the main characteristic of this syndrome is a hyperexcitability state characterized by a greater tendency to convulsions independent of the pattern and nature of the elicitor stimuli (Essig 1967; Kalant et al. 1971). Thus, it seems that both the increase in seizure susceptibility and the increment in general activity of withdrawn rats are simply a manifestation of CNS supersensitivity induced by the long-term drug depression (Sharpless 1969). According to Sharpless (1964), this phenomena is probably a compensatory mechanism developed against the long-term depressant effect of the drug, induced perhaps to maintain homeostasis. Indeed, withdrawal signs were not detected in rats after gradual withdrawal from long-term haloperidol treatment (Bernardi & Palermo-Neto 1979). Furthermore, comparing the effects of single and long-term haloperidol administration, the author observed a correlation between the impairment of motor function induced by different doses of haloperidol, singly administered, and the increment of general activity observed after withdrawal from long-term neuroleptic administration (Bernardi et al. 1981).

It is important to emphasize concern that the author is referring to postsynaptic supersensitivity, also named "denervation" or "disuse" supersensitivity, where the major synaptic change involved is at the postsynaptic receptors (Tarsy & Baldessarini 1974). Specificly, the author believes that, in his experiments, the long-term interrup-

[1]Laboratory of Pharmacology and Toxicology, Faculty of Veterinary Medicine, University of São Paulo, SP, Brazil.

Send correspondence to Dr. Palermo-Neto at Faculdad de Medicina Veterinaria USP, Farmacologia Aplicado e Toxicologia, Av. Corifeu de Azevedo Marques, 2720, 05340 São Paulo, SP, Brazil.

tion of synaptic transmission resulted in supersensitive receptors to the endogenously released neurotransmitter or to its related agonists. This hypothesis seems true. Indeed, haloperidol blocks postsynaptic dopaminergic receptors (Ljungberg & Ungerstedt 1977) and diphenylhydantoin, ethanol, and sodium barbital interfere with synaptic transmission in presynaptic terminals blocking different processes of Ca^{++}-dependent neurotransmitter release, such as noradrenaline (Blaustein 1976; Pincus & Lee 1973; Williams et al. 1975). In this respect, catecholaminergic systems are related both to general activity (Dunstan & Jackson 1976) and to convulsion spread (Jobe et al. 1973). Further, it was shown that noradrenaline plays an important role in barbiturates withdrawal (Morgan et al. 1978; Tabakoff et al. 1977).

Thus, it seems that hyperactivity, a classic and insufficiently explored symptom of early drug withdrawal (Martin 1977), is one of the many behavioral manifestations of CNS supersensitivity. So, quantification of these behaviors in an open field displays the phenomena. Indeed, as sound or high levels of illumination inside the apparatus were not used, it is supposed that the subject will habituate to, and hence be minimally influenced by, aspects of test situations other than the specific stimulus component being used as the independent variable, in the author's studies, drug withdrawal.

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Tiapride in Tardive Dyskinesia

D.J. Murphy, M.R.C. Psych.,[1] G. Hughes, M.B. B.Sc.,[1] and G.K. Shaw, F.R.C. Psych.[1]

Introduction

Tardive dyskinesia is manifested by a wide variety of involuntary movements including orolingual dyskinesia, chorea, athetosis, dystonia, tics, and facial grimacing, but excluding rhythmic tremor (APA Task Force Report, 1980). There is substantial evidence that the pathogensisi of tardive dyskinesia relates to chronic dopamine receptor blockade produced by long-term administration of antipsychotic drugs (Gardos & Cole 1980).

Drug treatment of tardive dyskinesia has been ineffective (Editorial, *Br. Med. J.* 1981). Many clinical trials demonstrate improvement in a proportion of patients but few patients in any given trial have shown more than 50 percent improvement (Gardos & Cole 1980).

Tiapride (N-diethylaminoethyl methoxy-2-methyl sulphonyl-5-benzamide hydrochoride) is closely related structurally to both metoclopramide and the antipsychotic drug sulpiride. It differs from typical neuroleptics in animals models for neuroleptic activity: it fails to induce catalepsy, displays weak sterotypy antagonism, weak ability to displace neuroleptic ligands, and inactivity in inhibiting dopamine sensitive adenylate cyclase (Jenner et al. 1978).

It inhibits perioral dyskinesias induced by the striatal injection of dopamine in animals (Costall & Naylor 1977), reduces levodopa-induced peak dose involuntary movements (Lees et al. 1979), and produced a marked improvement in buccofacial dyskinesia in the elderly (Courrier et al. 1978). In the present study the antidyskinetic potential of tiapride was examined on chronic psychiatric patients with tardive dyskinesia.

Method

Eight patients were selected from the wards of a large psychiatric hospital. They all had a case-note diagnosis of chronic schizophrenia. Their clinical features and medication history are summarized in Table 1. It was not possible to discover the length of time for which dyskinesia had been present, but it was not less than 5 years in any patient. Likewise, exact duration of neuroleptic therapy was difficult to establish but was never less than 20 years. All patients displayed involuntary movements of the orolingual or facial musculature. While the authors were inexperienced in neurological practice, efforts were made by case-note perusal and clinical evaluation to exclude patients with a neurological disorder (other than tardive dyskinesia) or those displaying stereotyped movements of schizophrenia. Baseline psychotropic medication remained unchanged for the 6-week trial period, and during the trial no patient received any other medication affecting dopaminergic or cholinergic neurotransmission. Tiapride was administered in three daily doses at 8:00 a.m., 1:00 p.m., and 6:00 p.m. Dosage is recorded in Table 2. The dose was increased after a week if response was not marked.

Movements were recorded by video-filming in a standardized manner as described by Kidger et al. (1980) at the same time of day (afternoon) each week. The scoring format for abnormal movements by Kidger et al. (1980) was used by the authors who jointly viewed the tapes. Filming was done before tiapride was introduced and thereafter at weekly intervals before dosage was

[1]Bexley Hospital, Bexley, Kent, England.

Address for reprint requests and correspondence: Dr. D.J. Murphy, University of Michigan Hospital, Department of Psychiatry, Clinical Studies Unit, Ann Arbor, MI 48104.

increased and at the conclusion of the trial. Parkinsonian effects were measured using the rating scale of Simpson and Angus (1970) before the start and at the conclusion of the study.

Results

The effects of treatment are summarized in Table 2. At the conclusion of week 6, when all but one patient were on 600 mg of tiapride per day, one patient was worse, three were marginally worse, one remained the same, two were marginally improved, and one was improved. Mean dyskinesia score before treatment was 4.13 ± 1.81 S.D.: at maximum dosage of tiapride was 4.25 ± 1.83 S.D. (not statistically significant). During the course of the trial, seven of the eight patients did show improvement on initial ratings but this was not maintained. One patient was noticed to have ceased a grunting sound which he was accustomed to make which initially we had not considered to be a dyskinetic phenomenon but in retrospect might have been due to diaphragmatic dyskinesia. Another patient not rated as improved was reported by nursing staff to be able to hold a cigarette in her mouth which she had not been capable of previously. In patients 2, 6, and 7, the dose of tiapride was increased to 800 mg per day for 2 days only after week 6 with marginal improvement in one patient only. The mean parkinsonism score rose from 8.75 ± 5.50 S.D. to 10.86 ± 4.74 S.D. at maximum dose of tiapride (not significant: Student's *t*-test), but this did not seem to impair everyday activities. One patient dropped out of the trial because of transfer to a hostel and in another the full dosage increase was not possible because of hypotension. No marked changes in mental state were noted in any patient.

Discussion

The results of the investigation suggest that tiapride does not have a clinically significant antidyskinetic action in patients with chronic tardive dyskinesia. The work was prompted by the theory that there are two different populations of dopamine receptors in the striatum (Jenner & Marsden 1979), those whose blockade caused neuroleptic-induced parkinsonism and those whose hypersensitivity is responsible for dyskinetic movements (Costall & Naylor 1977). The failure of tiapride to influence these receptors

Table 1

Patient Data and Baseline Medication

Patient No.	Sex	Age	Approximate Duration of Previous Neuroleptic Treatment (years)	Neuroleptics During Investigation	Anticholinergics During Investigation
1	M	56	20	Clopenthixol 800 mg I/M 2-weekly	Procyclindine 10 mg daily
2	M	53	20	Haloperidol 12 mg daily	Procyclidine 15 mg daily
3	M	66	24	None	Procyclidine 5 mg daily
4	M	64	20	Clopenthixol 100 mg I/M 3-weekly	Procyclidine 10 mg daily
5	M	61	25	Clopenthixol 200 mg I/M 3-weekly	Procyclidine 10 mg daily
6	F	65	25	None	None
7	M	65	20	Fluphenazine Decanoate 75 mg I/M 3-weekly	Procyclidine 10 mg daily
8	M	74	25	Thioridazine 225 mg daily	None

in the dose-dependent manner expected from a mechanism of postsynaptic blockade poses some questions. Was this a condition in which irreversible changes had taken place? This seems likely. Marsden et al. (1975) reported that the risk of permanent tardive dyskinesia was around 30 percent of those developing the problem and the general ineffectiveness of treatment has been alluded to previously. However, sulpiride, which is similar to tiapride, was reported to reduce tardive dyskinetic movements in a dose-dependent manner by Casey et al. (1979). Differences between Casey's group and that of the authors' study were that his subjects had a lower mean length of neuroleptic treatment, and only 5 of his 11 subjects had a diagnosis of schizophrenia.

The finding of a nonsignificant increase in parkinsonism is in accordance with Casey et al.'s results with sulpiride lending indirect support to the theory of subpopulations of striatal dopamine receptors. However, at variance with the findings are those of Lees et al. (1979) and L'Hermitte et al. (1977) who found a marked increase in parkinsonism with smaller doses of tiapride albeit in patients with idiopathic parkinson's disease. The finding that levodopa induced peak dose movements were reduced in the studies of Lees et al. (1979) and L'Hermitte et al. (1977) underlines differences in the pathophysiology of the two conditions.

Reservations about the general applicability of the findings are as follows. A small group of elderly subjects were used, most of whom remained on neuroleptic and anticholinergic medication which may have affected the action of tiapride. A rating scale was used which measured the site and duration of movements and not the intensity. Perhaps the dose was increased too rapidly. A greater response might have been obtained at higher doses than were used. The investigators feel that further preliminary studies are warranted, particularly on a less chronic population.

Table 2

Dosage, Tardive Dyskinesia, and Parkinsonism Scores

Patient No.	Dose[a] T.D. Score[b]	Before Tiapride	Duration of Treatment (Weeks)						Parkinsonism Score[c]	
			1	2	3	4	5	6	Before Tiapride	At Maximum Dose of Tiapride
1	Dose		76	150	150	150	300	600	1	8
	T.D. Score	5	7	2	2	6	2	6		
2	Dose		75	150	300	600	600	600	13	17
	T.D. Score	7	1	4	4	2	3	3		
3	Dose		75	150	300	600	600	600	8	11
	T.D. Score	2	2	6	5	2	2	6		
4	Dose		75	75	75	150	300	75	8	15
	T.D. Score	2	0	1	2	1	3	3		
5	Dose		75	150	300	300			16	—
	T.D. Score	4	4	1	3	3				
6	Dose		75	150	300	600	600	600	6	7
	T.D. Score	6	7	6	5	4	5	7		
7	Dose		75	150	300	600	600	600	3	4
	T.D. Score	4	3	6	1	2	4	4		
8	Dose		75	75	75	150	300	600	15	14
	T.D. Score	3	0	2	2	3	1	2		

[a] Total daily dose of tiapride (mgs)

[b] On scale of Kidger et al.

[c] On scale of Simpson and Angus.

Conclusion

Tiapride, a substituted benzamide derivative closely related to metoclopramide, failed to have a marked beneficial effect in seven of eight patients in a 6-week open study on patients with chronic tardive dyskinesia. Despite the use of high doses, increase in parkinsonian symptoms was not significant, lending support to the notion of separate groups of dopamine receptors. The authors' results underline the intractability and possible irreversibility of the syndrome.

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Articles—

Haloperidol Plasma/Red Blood Cell Ratios and Clinical Efficacy[1]

Robert Neborsky, M.D.,[2] David S. Janowsky, M.D.,[2] James Perel, Ph.D.,[3] Ethan Munson, D.O., B.A.,[2] and Dennis Depry, M.D.[2]

Introduction

Although the ability to accurately measure serum and red blood cell (RBC) levels of antipsychotic agents and their metabolites by a variety of techniques has advanced greatly during the past decade (Clark et al. 1977; Cohen & Hershel 1979; Creese & Snyder 1977; Hornbeck et al. 1979; Rubin et al. 1980), utilization of these analytic techniques to assess which dose of a given neuroleptic is indicated in a specific patient has been less useful than originally hoped for, although several studies have suggested some relationship between serum and/or RBC levels of neuroleptics and clinical efficacy (Casper et al. 1980; Davis 1980).

The present study is part of a previously reported experiment designed to evaluate the relationship of high- and relatively low-dose haloperidol administration to outcome in acutely ill psychotic inpatients (Neborsky et al. 1981). In this study, the relationship of plasma and RBC levels of haloperidol, as well as the relationship of the ratio of plasma to RBC haloperidol levels to antipsychotic efficacy, has been studied.

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[2]Departments of Psychiatry, University of California, San Diego and San Diego Veterans Administration Medical Center, La Jolla, CA 92093.

[3]Western Psychiatric Institute and Clinic, Pittsburgh, PA 15261.

Method

In a study (Neborsky et al. 1981) intended to investigate the effects of rapid neuroleptization and subsequent short-term maintenance with low- and high-dose haloperidol, a total of 20 acutely psychotic male inpatients were utilized. Although originally diagnosed by Diagnostic and Statistical Manual-II (DSM-II) criteria, these subjects were later diagnosed retrospectively by DSM-III criteria. Based on the later criteria, the following was found: schizophreniform disorder, $N = 11$; brief reactive psychosis or schizophreniform disorder, $N = 1$; schizophrenic disorder, paranoid type, $N = 1$, schizophrenia, undifferentiated type, $N = 5$; major affective disorder, manic episode, $N = 2$.

Of these 20 subjects, 10 were randomly assigned to a 10 mg dose haloperidol treatment group and 10 patients were assigned to a 2 mg dose haloperidol treatment group. Each patient then received a series of double-blind haloperidol administrations in a three-phase sequence. Treatment Day 1 was subdivided into two phases (Phases I and II). During Phase I, which consisted of an intramuscular rapid neuroleptization phase, patients received at least 1 and up to 5 hourly injections of haloperidol, given until tolerance for oral medication was possible. During Phase II, the oral rapid neuroleptization phase, the patients received the same 2 mg dose or 10 mg dose of oral haloperidol, respectively, as they had received in Phase I, up to a maximum of

four additional doses. At 8:00 a.m. the following day, the patients were entered into Phase III, the oral maintenance phase, which lasted for 6 more days. During this phase, the patients received a total number of 2 or 10 mg doses each day. This data is equal to the total administered during Phase I plus II. However, the treating physician was permitted to blindly alter the number of dosages based on behavioral observations. Table 1 displays the mean milligrams of haloperidol administered during each of the three phases.

Table 1

Milligrams Haloperidol Administered During Three Experimental Phases Expressed as Mean ± SEM

Dosage	Phase I[a]	Phase II[b]	Total of Phase I + II	Average Daily Dose During Phase III[c]
2 mg/dose	8 ± 0.6	2 ± 0.5	10 ± 0.6	12 ± 0.7
10 mg/dose	29 ± 2.0	14 ± 4.0	45 ± 3.0	38 ± 4.0

[a] Phase I = Rapid Intramuscular Neuroleptization Phase
[b] Phase II = Rapid Oral Neuroleptization Phase
[c] Phase III = Oral Maintenance Phase

Behavioral responses to treatment were measured in part using the Brief Psychiatric Rating Scale (BPRS) of Overall and Gorham (1962). The BPRS was completed at baseline, and at the end of Phase III. Daily 9:00 a.m. bloods were drawn in heparinized tubes, centrifuged, separated into plasma and RBC fractions (which were allowed to lyze), and frozen at −40°C. Selected plasma and RBC samples were measured for haloperidol levels from the same sample by the radioimmunoassay technique of Perel et al. (1981) and Shostak and Perel (1976). Although the majority of the blood samples analyzed for this report were drawn on the last day of Phase III, certain samples analyzed were drawn on other days due to sample loss (mean day ± SEM = 6.85 ± .27).

Results

As described previously, there was no difference in overall clinical outcome between the high- and low-dose haloperidol treatment groups (Neborsky et al. 1981). Regardless of dosage, early clinical improvement during the first day of treatment (Phases I and II) predicted eventual improvement at the end of Phase III (Neborsky et al. 1982). Despite no overall dose-related differences in improvement between treatment groups in clincial outcome, there were substantial differences in improvement within groups (Neborsky et al. 1982). Some patients' symptoms nearly returned to a remitted baseline state, while others were completely refractory to treatment.

In examining the relationship between measured haloperidol levels, plasma and RBC haloperidol levels were found to differ significantly between the high- and low-dose groups. The high-dose group's plasma levels averaged 33.9 ± 5.0 ng/ml (mean ± SEM) and the high-dose RBC levels averaged 40.8 ± 5.7 ng/ml, whereas the low-dose groups averaged 8.2 ± 0.8 ng/ml and 9.3 ± 1.0 ng/ml, respectively. The average oral dose administered to each patient correlated significantly with the average plasma ($r = .639$, $p < .001$), and RBC concentrations ($r = .759$, $p < .001$), and a strong correlation between plasma and RBC haloperidol concentrations ($r = .975$, $p < .001$) was also found.

As shown in Table 2, there was no significant correlation of either plasma or RBC haloperidol levels with either baseline, or absolute or percent

Table 2

Correlations of Haloperidol Plasma Levels, Red Blood Cell Levels, and Plasma/Red Blood Cell Ratios with Clinical Improvement After 7 Days of Treatment in 20 Acutely Psychotic Psychiatric Inpatients

	Baseline BPRS Scores	Absolute Improvement in BPRS	Percent Improvement in BPRS
Plasma Concentration of Haloperidol	.061	.109	.101
Red Blood Cell Concentration	.085	−.023	−.064
Plasma/Red Blood Cell Ratio	−.126	.496[a]	.640[c]
Red Blood Cell/Plasma Ratio	.141	−.560[b]	−.715[c]

[a] = $p < .05$
[b] = $p < .01$
[c] = $p < .001$

improvement in psychopathology, as measured by the BPRS change scores between the baseline an the end of the maintenance phase. In contrast, the ratio of either plasma to RBC or RBC to plasma haloperidol concentrations demonstrated a strong and statistically significant correlation with both the absolute BPRS change scores and the percent change in the BPRS from the beginning to the end of the study, but did not correlate at all with baseline BPRS scores. The ratios showed a range from 0.907 to 1.599 for the RBC/plasma ratio, and from 0.625 to 1.103 for the plasma/RBC ratio. The range of the plasma/RBC haloperidol ratios and their relationship to improvement on the BPRS are displayed in the Figure.

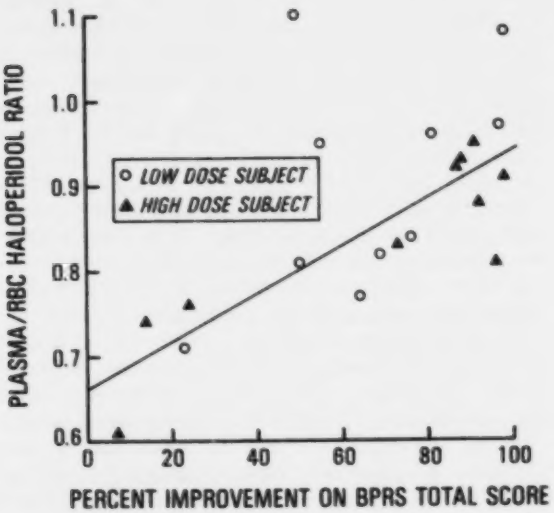

FIGURE. The relationship of plasma/RBC haloperidol ratios to percent improvement in the BPRS following 7 days of treatment in 20 acutely psychotic inpatients.

Discussion

The results are unsupportive, at least in acutely ill psychotic psychiatric inpatients, of the assertion that haloperidol dose and plasma and RBC haloperidol levels as such are useful indicators of clinical efficacy, at least when clinically accepted doses of haloperidol are utilized. This observation is different from that of some others who reported dose-effect relationship between haloperidol levels and efficacy (Calil et al. 1979; Ericksen et al. 1978; Forsman et al; 1977; Magliozzi et al. 1981; Tune et al. 1980). The reason for this difference is difficult to accurately appraise, because of study design variations and patient sampling differences between studies, but it is clear that the study was of very short duration, lasting only 7 days. If the study had been carried out for a longer time, or with a larger number of patients, a more classic dose response curve might have become apparent. Another difficulty with the study is that it was not a fixed-dose study, so that with each dosage group, respectively, an artificial triphasic relationship could have been produced (Cohen & Baldessarini 1981; Neborsky et al. 1981). A further difficulty in the design is the fact that the patients may not have reached steady-state blood levels, so that the oral dose to blood level correlations may be misleading (Forsman & Ohman 1975, 1976). A final weakness of this study is the fact that the patient group, although all psychotic, was diagnostically mixed, and was generally acute, rather than chronic schizophrenics. It is conceivable that a more homogenous group of subjects, or subjects with a poorer prognosis, would not have shown the significant correlations between plasma/RBC haloperidol ratios and clinical outcome.

Nevertheless, the observation that plasma/RBC haloperidol ratios may reflect clinical efficacy, regardless of dose, may have potential theoretical and practical implications. If plasma/RBC haloperidol ratios, analyzed early in treatment of a patient are found to eventually predict efficacy data, a valuable clinical tool may be developed. Furthermore, it is possible that *in vitro* techniques for examining plasma/RBC neuroleptic level ratios, prior to initiating neuroleptic treatment, may offer a clinical tool for prediction of response to neuroleptic therapy beyond the trial and error methods currently in use.

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Cholinomimetic-Induced Co-Release of Prolactin and Beta-Endorphin in Man[1]

S. Craig Risch, M.D.,[2,4] David S. Janowsky, M.D.,[2,4] Larry J. Siever, M.D.,[3] Lewis L. Judd, M.D.,[2] Jeffrey L. Rausch, M.D.,[2] Leighton Y. Huey, M.D.,[2,4] Kimberlee A. Beckman,[2] Robert M. Cohen, M.D.,[3] and Dennis L. Murphy, M.D.[3]

The endorphins have been mechanistically implicated in the hypothalamic modulation of anterior pituitary prolactin release, presumably by affecting hypothalamic neurotransmitter activity regulating anterior pituitary prolactin release mechanisms (Meites et al. 1979; Van Vugt & Meites 1980). In animal studies (Gold et al. 1979; Grandison & Guidotti 1977; Rivier et al. 1977b; Shaar & Clemens 1980; Van Vugt & Meites 1980) and human studies (Catlin et al. 1980; Extein et al. 1980; Schulz et al. 1980), the intravenous or intraventricular administration of beta-endorphin or exogenous opioids, such as morphine or methadone, produce dose-dependent increases in plasma prolactin concentrations. Similarly, in animal studies, administration of the opiate receptor antagonist, naloxone, may depress basal plasma prolactin concentrations, as well as attenuate or block endogenous or exogenous opioid-associated increases in plasma prolactin concentrations (Grandison & Guidotti 1977; Guidotti & Grandison 1978; Meites et al. 1979; Rivier et al. 1977b; Shaar & Clemens 1980; Van Vugt & Meites 1980).

These studies suggest that the endogenous opioid peptides may be important in the normal physiological regulation of anterior pituitary prolactin release.

It is believed that endogenous opioid peptide effects on anterior pituitary prolactin release are probably not due as such to direct effects on hypothalamic hormones regulating pituitary function (Meites et al. 1979), nor are they believed to be due to a direct opioid effect on the pituitary, since beta-endorphin does not stimulate prolactin release from hemipituitaries (Shaar et al. 1977) or from cultured pituitary cells (Rivier et al. 1977a, 1977b). Rather, it is currently hypothesized that endogenous opioid peptides modulate anterior pituitary prolactin release via actions on hypothalamic neurotransmitters such as dopamine and serotonin, which in turn regulate the release of hypothalamic hormones into the hypothalamic pituitary portal vasculature. Specifically, beta-endorphin has been demonstrated to reduce medial basal hypothalamic concentrations of dopamine, both *in vivo* (Deyo et al. 1979; Van Loon et al. 1980a; 1980b; Van Vugt et al. 1979) and *in vitro* (Enjalbert et al. 1979; Wilkes & Yen 1980). In addition, other studies have suggested that endorphins and enkephalins may increase brain serotonin turnover (Algeri et al. 1978; Van Loon & De Souza 1978), and may thereby modulate anterior pituitary prolactin release (Cusan et al. 1977; Spampinato et al. 1979).

In addition, considerable evidence, albeit conflicting, suggests a relationship between central acetylcholine and plasma prolactin activity. In a series of animal experiments by Grandison et al. (1974) and Grandison & Meites (1976), centrally or systemically administered cholinomimetics reduced basal prolactin levels, reduced the daily nocturnal surge of prolactin, reduced prolactin rises in female rats or estrogen-treated male rats

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[2]Department of Psychiatry, School of Medicine, University of California at San Diego, La Jolla, CA 92093.
[3]Clinical Neuropharmacology Branch, National Institute of Mental Health, Bethesda, MD 20205.
[4]Psychiatry Services, San Diego Veterans Administration Medical Center, San Diego, CA 92161.

at proestrus, and reduced prolactin rises subsequent to stress, ether, or 5-hydroxytryptamine (5-HTP) administration. Subramanian and Gala (1976) also report that both nicotinic and muscarinic cholinergic agonists prevent the afternoon circadian surge in ovariectomized, estrogen-treated rats. However, in the same study (Subramanian & Gala 1976), these investigators noted that high doses of atropine also attenuated this afternoon surge of prolactin in ovariectomized, estrogen-treated rats. McLean and Nikitovich-Winer (1975) also reported that high-dose atropine in animal studies inhibited the nocturnal rise in prolactin secretion, an effect which could be blocked by pretreatment with physostigmine. Libertun and McCann (1973) similarly reported that intraventricular or subcutaneous atropine could inhibit prolactin release in rats. In contrast, Lawson and Gala (1975), using cholinergic receptor agonists and antagonist pharmacological probes in animal studies, were unable to demonstrate any effect of these agents on basal prolactin levels.

In spite of the varying effects of cholinomimetic drugs on plasma prolactin levels in animals, the intravenous administration of centrally active cholinomimetics, such as physostigmine, an acetylcholinesterase inhibitor with both nicotinic and muscarinic cholinomimetic properties, or arecoline, a relatively selective muscarinic agonist, consistently produces significant increases in plasma prolactin, as well as beta-endorphin immunoreactivity in human subjects (Risch et al. 1980, 1981).

From these human results, these investigators have hypothesized that the cholinomimetic-induced increases in prolactin concentrations, observed in these investigators' previous studies, might reflect cholinergic activation of hypothalamic beta-endorphin release mechanisms as described above.

These investigators now describe three separate studies in three groups of human volunteer subjects in which centrally active cholinomimetic agents and placebo controls are used to define correlations between cholinomimetic-stimulated increases in hypothalamic-pituitary release of beta-endorphin and increases in plasma prolactin concentrations.

Method

In three separate experiments, the relationship of physostigmine as well as arecoline-induced increases in plasma prolactin and beta-endorphin immunoreactivity was studied. In the first experiment, nine normal volunteers (5 male, 4 female, ages 18-29) at the National Institute of Mental Health (NIMH) received physostigmine salicylate 33 μg/kg and saline placebo. In the second experiment, eleven normal volunteers (all male, ages 21-30) at the University of California at San Diego received physostigmine salicylate 22 μg/kg and saline placebo. In the third experiment, six normal volunteers (2 male, 4 female, ages 19-28) at the NIMH received arecoline hydrobromide (3 mg) and saline placebo.

All three studies were conducted under a Food and Drug Administration-approved investigational new drug (IND) and with local Human Subjects Committee approval, and all subjects gave written informed consent. Studies were conducted between the hours of 8:00 a.m. and 11:00 a.m. under randomized, double-blind conditions in which subjects, after pretreatment with methscopolamine 1.0 mg intramuscular (i.m.) or glycopyrrolate 0.2 mg intravenously (i.v.) received either placebo (normal saline) or active drug (physostigmine 22 μg/kg or physostigmine 33 μg/kg or arecoline 3.0 mg), as described above, on 1 day and received the other condition at least 2 days later, given over a 10-minute period. In each study, after an adaptational period of 30 minutes subsequent to the insertion of an indwelling heparin lock catheter, subjects had blood samples for neuroendocrine measurements drawn at 30, 15, and 0 minutes prior to active drug or placebo infusion, and at 10, 20, 35, and 50 minutes subsequent to each 10-minute infusion.

Plasma concentrations of beta-endorphin and prolactin were determined by radioimmunoassay as previously described (Kalin et al. 1981; Risch et al. 1980, 1981). The antibody for beta-endorphin demonstrates a 50 percent cross-reactivity, with beta-lipotropin, but less than 0.01 percent with alpha-endorphin, alpha-MSH, and less than 0.004 percent with leucine enkephalin and methionine enkephalin. Within-assay variability for beta-endorphin is approximately 56 percent and sensitivity is 25-50 pg/ml. The antibody for prolactin has cross-reactivities of hTSH <0.3 percent, hLH <0.1 percent, hFSH <1 percent, and hGH <0.03 percent. Within

assay, variability for prolactin is approximately 5 percent and sensitivity is 5 ng/ml. In each of the three studies, all samples for plasma beta-endorphin or prolactin determinations were assayed within the same assay.

Significance of changes in plasma beta-endorphin and prolactin immunoreactivities were determined by repeated measures analysis of variance. Linear regression analyses were performed to determine the relationships and significance of cholinomimetic-induced changes in plasma prolactin and beta-endorphin immunoreactivities within individual subjects.

Results

In Experiments 1 and 2, highly significant increases in plasma beta-endorphin and prolactin immunoreactivity occurred after physostigmine infusion, but not after placebo, similar to those previously reported by these investigators (Risch et al. 1980, 1981). Changes in plasma concentrations of beta-endorphin and prolactin immunoreactivities subsequent to physostigmine were highly correlated, as described in Figures 1 and 2.

Similarly, in Experiment 3, significant increases in plasma beta-endorphin and prolactin immunoreactivities also occurred after arecoline, but not after saline placebo. As with the physostigmine infusions, changes in plasma concentrations of beta-endorphin and prolactin immunoreactivities subsequent to arecoline infusion were highly correlated, as illustrated in Figure 3.

Discussion

In three separate studies, changes in plasma concentrations of beta-endorphin were highly correlated with changes in plasma concentrations of prolactin. In addition, as depicted in Figures 1, 2, and 3, there were no increases in plasma prolactin concentrations in the absence of increases in plasma beta-endorphin concentrations. Although high correlations between exogenously administered opioids and subsequent prolactin release have been previously reported, this is the first report of such an association between endogenously stimulated opioids and changes in plasma prolactin concentrations.

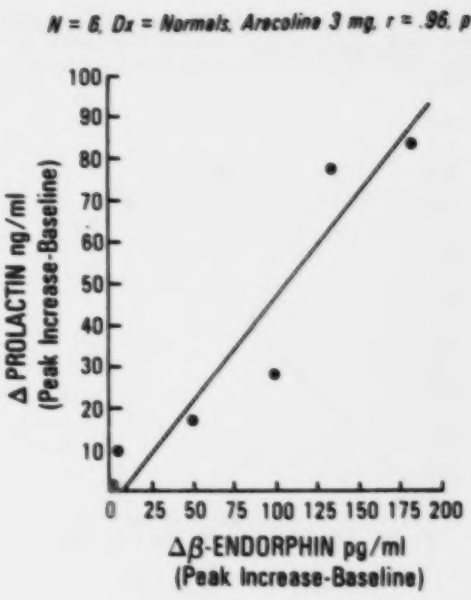

FIGURE 1

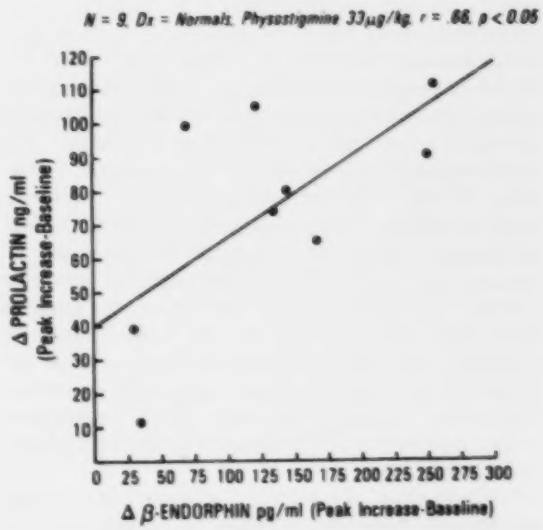

FIGURE 2

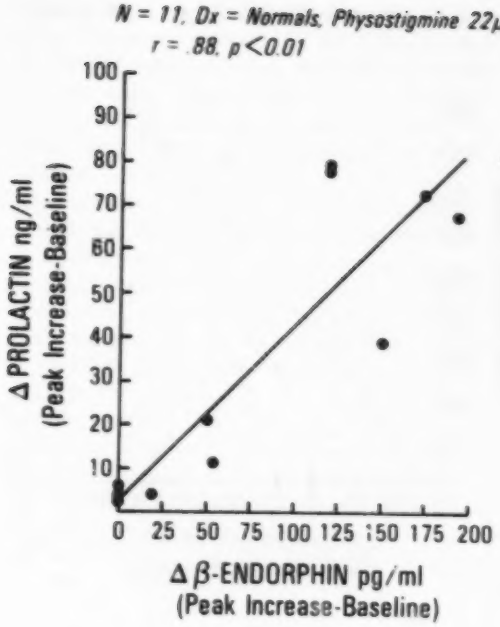

FIGURE 3

As reviewed above, these high correlations may reflect central cholinergically stimulated beta-endorphin modulation of anterior pituitary prolactin release. However, the high correlations between plasma beta-endorphin and prolactin increases do not necessarily prove that the observed increases in beta-endorphin release are mechanistically involved in the prolactin elevations. If the proposed model is correct, pretreatment of subjects with naloxone, a specific opioid antagonist, might be expected to block or attenuate the endorphin stimulation of anterior pituitary prolactin release. However, the authors have been reluctant to use the combination of naloxone and physostigmine because a pilot experiment in their laboratory suggested increased cholinergic toxicity, although three subsequent larger studies in their laboratory failed to replicate this finding.

Nevertheless, the authors believe that the high correlations between increases in plasma concentrations of beta-endorphin and prolactin observed in their studies provide a useful heuristic model for understanding the effects of centrally active cholinergic agents on anterior pituitary prolactin regulation. Furthermore, if the proposed model is correct, these findings may provide an interesting example of peptidergic modulation of primary neurochemical mechanisms involved in hypothalamic-pituitary prolactin regulation.

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Review

Hormonal and Neurotransmitter Hypotheses of Premenstrual Tension[1]

Jeffrey L. Rausch, M.D.,[2] David S. Janowsky, M.D.,[2] S. Craig Risch, M.D.,[2] Lewis L. Judd, M.D.,[2] and Leighton Y. Huey, M.D.[2]

Introduction

The incidence of premenstrual-menstrual psychologic symptoms (premenstrual tension) has been estimated as between 25 and 100 percent of all women (Janowsky et al. 1971), with severity ranging from mild irritability to frank psychotic episodes (Endo et al. 1978; Smith et al. 1976). Symptoms are usually confined to the 5 days prior to menstruation, and abate with the onset of menses or shortly thereafter (Smith 1971). However, increases in negative affect have been found to occur as early as 11 days prior to menstruation, and to continue well into the menstrual phase (Janowsky et al. 1973), although these symptoms are to be distinguished from dysmenorrhea, a syndrome of menstrual pain etiologically associated with prostaglandin levels (Chan & Dawood 1980; Pickels 1979). A variety of hypotheses have been employed to explain the etiology of premenstrual tension (PMT) syndrome. Speculations have ranged from the psychosocial to the biochemical, but to date no single hypothesis has proven altogether satisfactory. This article reviews several of the major biological hypotheses concerning the etiology of premenstrual tension.

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[2]Departments of Psychiatry, University of California, San Diego and San Diego Veterans Administration Medical Center, La Jolla, CA 92093.

The Ovarian Hormone Hypothesis

In 1931, Frank first described the premenstrual tension syndrome and postulated its hormonal pathogenesis, a hypothesis now widely accepted, and deriving considerable support from animal as well as human studies. The ovarian hormones, progesterone and estrogen, are the two hormones which have been most widely studied with respect to premenstrual tension. Various theories have been proposed as to how alterations in these hormones may be etiologic.

Low progesterone levels have been considered etiologic of premenstrual tension. Mundy et al. (1977) studied 16 women, half of whom suffered from premenstrual tension. At 5 to 8 days prior to menstruation, the mean plasma progesterone for the premenstrual tension groups was 31 ± 10 nanomoles per liter as compared with the 45 ± 14 nanomoles per liter for the control group. These findings are comparable with those of Bäckström and Carstensen (1974), who found that in women with predominately psychological premenstrual symptoms, progesterone levels were reduced and estrogen levels increased, as compared with normal women during the week prior to menstruation. Smith (1976) reported small but significant differences in progesterone levels in sufferers of premenstrual depression, with the symptomatic group showing slightly lower progesterone levels, as compared with those of normal women during the week preceding menstruation. O'Brien et al. (1979), however, reported significantly higher levels of progesterone 10 days prior to menstrua-

tion in symptomatic women, as compared with controls although, at 4 days prior to menstruation in that study, the symptomatic group's mean progesterone level was nonsignificantly lower than the mean for the control group.

Premenstrual-menstrual emotional symptoms may be related to falling levels of progesterone. Dysphoric emotional symptoms often begin in the luteal phase but intensify as progesterone drops from its highest levels during the luteal peak to its relatively low premenstrual level. Also, induction of depressive symptoms have been reported following withdrawal of exogenous progesterone treatment (Hamburg 1966). Dysphoria occurs in the third trimester of pregnancy, when progesterone is elevated, and increases postpartum as progesterone levels fall (Helmer & Judson 1967; Treadway et al. 1969).

It has also been suggested that premenstrual-menstrual psychologic symptoms may be related to high estrogen levels per se. As with progesterone, an increased occurrence of psychologic symptoms occurs during the luteal phase of the cycle, when estrogen levels are high. Morton (1950) reported production of a premenstrual tension-like syndrome after intramuscular injection of estrogen. However, against this hypothesis, psychologic symptoms do not consistently increase at mid-cycle, when estrogen is most elevated, nor is there evidence of increased premenstrual symptomatology in women with endogenously prolonged or increased estrogen levels, such as occurs in metropathia hemorrhagia (Taylor 1977).

As with progesterone, estrogen withdrawal has been postulated as etiologic of premenstrual tension (Steiner & Carroll 1977) with increases in emotionality occurring in the premenstrual phase correlating with falling estrogen levels (Baird & Guevara 1969). However, the premenstrual fall in serum estrogen levels may not reflect central nervous system estrogen activity, since estrogen is selectively bound and concentrated in the limbic system and hypothalamus (Anderson & Greenward 1969).

It may be that absolute or falling levels of estrogen and/or progesterone are less important in the etiology of premenstrual tension than is the ratio of estrogen to progesterone. Greene and Dalton (1953) have specifically hypothesized a high estrogen/progesterone ratio as etiologic of premenstrual tension. They supported this hypothesis by noting that intramuscular progesterone alleviates the premenstrual syndrome (Dalton 1964; Rees 1953), a finding later challenged in a well-controlled study (Smith 1976).

As further support for an estrogen/progesterone ration hypothesis Bäckstrom and Carstensen (1974) noted that women with anxiety as the main premenstrual symptom had significantly higher estrogen levels premenstrually, as compared to a group of healthy women. In a later publication by Bäckström and Mattsson (1975), in 15 women with premenstrual tension, a positive correlation was found between the estrogen/progesterone ratio and anxiety.

Studies of the mood effects of oral contraceptives tend to associate irritability and anxiety with a high estrogen/progesterone ratio and depressive symptoms with a low estrogen/progesterone ratio (Culberg 1972). Indeed, these two hormones often have opposite central nervous system (CNS) effects with estrogen increasing running and mating behavior (Colvin & Sawyer 1969), increasing dorsal hippocampal excitability (Timiras 1971), and lowering seizure threshold (Wooley & Timiras 1962), and progesterone counteracting these effects, at least to some extent (Selye 1942, 1969).

In summary, the ovarian hormone hypothesis holds that premenstrual symptomatology is etiologically related to the ratios of progesterone and estrogen in the late luteal phase, or directly related to absolute or falling levels of progesterone or estrogen.

Several considerations make it difficult to completely implicate estrogen and progesterone in the ovarian-linked emotional disorders. Greene and Dalton (1953) found 17 percent of their 84 premenstrual tension sufferers attributing the onset of cyclic menstrual symptoms to the menopause—a time when estrogen and progesterone are relatively low. Also, any estrogen/progesterone ratio hypothesis must account for the relative absence of symptomatology present during the pre-ovulatory period, when serum estrogen levels are markedly higher than progesterone.

Mineralocorticoid Hypothesis

A major and enduring endocrine hypothesis as to the etiology of premenstrual tension implicates

the mineralocorticoids. From studies of normal women, there is some evidence that fluctuations of aldosterone may parallel the emotional fluctuations of the menstrual cycle. Aldosterone levels increase during the mid and late luteal phases, often to about twice that occurring during the follicular phase (Katz & Romth 1972; Reich 1962; Schwartz & Abraham 1975; Sundsfjord & Aakvaag 1972;), and at least one investigator has demonstrated premenstrual aldosterone peaks (Reich 1962).

The stimulus for increased aldosterone in the late luteal phase is not completely understood, but progesterone and the ovarian hormones have been implicated. Progesterone has been found to antagonize aldosterone and to cause a sodium diuresis, with a secondary increase in plasma renin activity and aldosterone secretion rates (Crane & Harris 1978). Sundsfjord and Aakvaag (1972), for example, found the pattern of increase and decrease in the plasma levels of aldosterone and plasma renin activity to be similar to those of plasma progesterone, suggesting that these fluctuations are causally related.

Aldosterone secretion may be altered in women suffering from premenstrual tension. Two early studies reported markedly increased premenstrual aldosterone excretion in symptomatic women (Janowsky et al. 1977; Perrini & Piliego 1959). However, more recent studies have failed to support these findings, in that Munday et al. (1977) found that the levels of plasma aldosterone in eight premenstrual tension patients were not consistently different from those of eight controls, despite a small surge of aldosterone in the late luteal phase. O'Brien et al. (1979), in a larger series of 28 women, found that the aldosterone level of symptomatic women on Day 24 was nonsignificantly lower than that of the control group's.

In a study indirectly measuring mineralocorticoid activity, Janowsky et al. (1973) evaluated changes in mood, weight, and urinary potassium/sodium (K^+/Na^+) ratio over a total of 15 menstrual cycles in 11 women in order to investigate whether these changes correlated in the same patients. The urinary K^+/Na^+ ratio was measured since there is evidence that, when dietary factors are controlled, this variable may in part reflect aldosterone and other mineralocorticoid effects. The data indicated that increases in negative affect, weight, and K^+/Na^+ ratio follow similar patterns in normal women when studied longitudinally. Thus, a statistically significant increase in urinary K^+/Na^+ ratio and negative affect occurred in the premenstrual phase of the cycle. The changes in the K^+/Na^+ ratio noted in this study strikingly paralleled the aldosterone excretion curve noted by Reich (1962).

Similarly, in a study of salivary samples from 30 menstruating females, DeMarchi and Tong (1972) found ovulatory and premenstrual increases in the K^+/Na^+ ratio. They noted that changes in salivary sodium and potassium composition have been observed in depressive illness, and that increased intraocular pressure has been found in women suffering from marked premenstrual tension. Finally, in support of a mineralocorticoid hypothesis of premenstrual tension, the aldosterone antagonist spironolactone has been reported to be more effective than placebo in decreasing symptoms of premenstrual tension (O'Brien et al. 1979).

In spite of the above information, some data do not support an aldosterone hypothesis of premenstrual tension. For example, as mentioned above, there is little evidence that the aldosterone activity in women with premenstrual tension is elevated. Also, other diseases such as Conn's Syndrome, associated with increased aldosterone levels, are not necessarily associated with emotional upsets.

It may thus be reasonable to hypothesize that a substance which fluctuates in parallel with aldosterone may cause the cyclic behavioral changes. Angiotensin may be a reasonable candidate for this substance, since angiotensin is an endogenous compound which probably stimulates aldosterone secretion, being activated itself in turn by renin. Angiotensin is elevated during the luteal phase of the menstrual cycle (Janowsky et al. 1971). Increases in renin activity are also found during the second half of the luteal phase (Kaulhausen et al. 1973).

Angiotensin exerts effects on animal behavior, central neurotransmitters, and autonomic functioning (Janowsky et al. 1971). It causes increased drinking behavior when given by vertegral artery infusion or intraventricularly (Fitzsimons & Simons 1969). This appears to be a cholinergic effect which can be antagonized by atropine (Janowsky et al. 1977). Angiotensin counteracts the anesthetic effects of amobarbital (Paliac & Khairallah 1967), and decreases exploratory activity in mice when given intraventricularly (Capek et al. 1969). It disrupts learned passive

avoidance responses in rats, possibly from an effect on memory (Morgan & Routtenberg 1977). Furthermore, a central hypertensive effect has also been reported which appears to have cholinergic and adrenergic components (Severs et al. 1967, 1970). Immunohistochemical studies have revealed nerve fibers containing angiotensin in several different parts of the brain (Fuxe et al. 1976; Printz & Lewicki 1977), and a brain enzyme with a renin-like activity has been demonstrated (Genten & Speck 1978). The latter enzyme may be brain renin.

Prolactin Hypotheses

Like estrogen and progesterone, the pituitary hormone prolactin has been proposed as causative of the premenstrual tension syndrome (Andersen et al. 1977; Graham et al. 1978; Halbreich et al. 1976). It appears likely that prolactin levels fluctuate through the menstrual cycle, with peaks occurring at ovulation and later in the mid and late luteal phases (Tamura & Igarashi 1973). However, in some women, there appears to be little change throughout the cycle (McNeilly et al. 1973). Increased levels of prolactin have been reported in premenstrual tension patients as compared with normal controls (Halbreich et al. 1976).

Several pilot studies have suggested that bromocriptine, a dopamine agonist which decreases prolactin, may ameliorate premenstrual tension syndrome as well as premenstrual weight gain and breast enlargement (Graham et al. 1978). However, at least one well-controlled study has shown bromocriptine only equal to placebo in its efficacy in treating premenstrual tension, and others have shown no efficacy (Andersen et al. 1977; Graham et al. 1978). Furthermore, at least one study (Tamura & Igarashi 1973) suggests that prolactin does not increase in the luteal phases of anovulatory women, and Adamopoulos et al. (1972) have noted that premenstrual tension continues to occur during anovulatory cycles.

Monoamine Neurotransmitter Hypothesis

The monoamine neurotransmitters serotonin, norepinephrine, and dopamine have been widely implicated in psychiatric disorders (Barchas et al. 1978). Evidence is also available which implicates these monoamines in the pathophysiology of premenstrual tension.

Animal studies indicate that ovarian hormones and monoamines show overlapping behavioral effects. Like certain antidepressants, estrogen induces running behavior in rats (Colvin & Sawyer 1969) and, like reserpine, progesterone induces sedation in rats and other mammals (Selye 1969).

Brain monoamines and sex steroids show overlapping effects in the regulation of sexual behavior in rats. Reserpine and tetrabenazine, both monoamine depletors, may be substituted for progesterone in activating sexual behavior in estrogen-primed castrated female rats. In contrast, tricyclic antidepressant drugs and monoamine oxidase inhibitors (MAOIs) decrease sexual activation in estrogen/progesterone-primed castrated female rats, especially when brain serotonin is selectively increased (Meyerson & Sawyer 1968). Furthermore, selective depletion of rat brain serotonin induces sexual excitation, especially when brain catecholamines such as dopamine and norepinephrine are simultaneously elevated (Tagliamonte et al. 1969).

Ovarian hormones and monoamines also exhibit overlapping functions in regulating ovulation. Elevation of brain serotonin blocks superovulation in immature rats (Krodon 1969), and decreased norepinephrine levels inhibit physiological estrus as determined by vaginal smears (Airaksinen & McIsaac 1968). Norepinephrine administration into the third ventricle in large doses induces ovulation. Reserpine administration inhibits ovulation in the rat, and this effect is antagonized by the administration of MAOIs or dopamine (Sawyer 1952). Reserpine induces pseudopregnancy in rats when given systematically and following local hypothalamic administration, and this effect is also prevented by treatment with MAOI (Meyerson & Sawyer 1968; Sawyer 1952).

Dopamine appears to exhibit a very important role in the regulation of gonadotropin secretion. Small doses of dopamine, incubated *in vitro* in the presence of pituitary and hypothalamic tissue, induce the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (Kamberi 1970; Meyerson & Sawyer 1968). Kamberi (1970) and Schneider and McCann (1969) have recently found that administration of small doses of-

dopamine or relatively high doses of norepinephrine or epinephrine significantly increase blood LH levels, while serotonin causes an opposite effect (Tagliamonte et al. 1969).

Evidence is available to indicate that ovarian hormones exert an influence on MAO activity. Pharmacologic doses of estradiol are associated with decreased tissue MAO activity in rats (Collins et al. 1970; Wurtman & Axelrod 1963). Progesterone appears to increase tissue MAO activity in rats (Collins et al. 1970), and increase plasma MAO activity in amenorrheic females (Klaiber et al. 1971). Increased endometrial monoamine oxidase occurs in the late luteal phase of the menstrual cycle and in direct proportion to the progestin content of oral contraceptives (Grant & Pryse-Davies 1968). Conversely, Belmaker et al. (1974) have noted a decrease in platelet monoamine oxidase premenstrually, and these findings have been replicated by Wirz-Justice et al. (1975).

Changes in brain monoamine levels have been found to cyclically occur throughout the rat estrus cycle. Greengrass and Tounge (1971) reported that the concentration of all three monoamines decreased in the rat during estrus, a time when ovulation is being stimulated by luteinizing hormone. During metaestrus, under the influence of luteal progesterone, the monoamine neurotransmitters begin to rise toward their maximum, achieved at dioestrus when estrogen and progesterone are low.

Thus, there is evidence that alterations in monoamines may be linked to ovarian and adrenal hormone fluctuations, as well as to behavioral changes. On this basis, a catecholamine (norepinephrine/dopamine) hypothesis, and a serotonin hypothesis of premenstrual tension have evolved.

The effects of angiotensin, estrogen, and progesterone on catecholamine neurotransmitter activity have been demonstrated in a number of *in vitro* studies using neurophysiological preparations. Angiotensin can inhibit the uptake of tritiated norepinephrine by brainstem slices, perfused rat brain ventricles (Paliac & Khairallah 1967), and synaptosomes (Janowsky et al. 1971). Further, endogenous rat brain norepinephrine is lowered by intraventricular angiotensin administration (Capek et al. 1969). Estrogen itself decreases the amount of labeled pre-equilibrated tritiated norepinephrine released by electrically stimulated rat brain slices by more than 25 percent (Vogel et al. 1970).

Janowsky and Davis (1970) also reported that progesterone and estradiol block the uptake of labeled norepinephrine by synaptosomes, and that the passive efflux of pre-equilibrated norepinephrine from synaptosomes, which is slightly slowed by estradiol, is increased by progesterone. Estradiol and progesterone inhibited the uptake of tritiated dopamine and norepinephrine by synaptosomes. Progesterone (1×10^{-4}M) increased the rate of passive efflux of labeled dopamine and norepinephrine from synaptosomes, whereas estradiol (1×10^{-5}M) did not affect dopamine efflux.

In the intact female rat, exogenous estrogen has been shown to decrease hypothalamic norepinephrine. Increased norepinephrine and decreased dopamine turnover rates have been shown in the rat after castration, these effects being reversible with large doses of estradiol and progesterone. Increased dopamine turnover has been shown in the tuberoinfundibular region after estradiol (Fuxe et al. 1970). In the striaturm, chronic estradiol administration increased the density of rat dopamine receptors, and increased behavioral sensitivity to amphetamine and apomorphine stereotypy, one of many effects estrogen can have on neurotransmitter receptors (*see* McEwen et al. 1981).

Norepinephrine and dopamine are metabolized enzymatically, in part, by catechol-o-methyltransferase (COMT), and this enzyme's activity has been inhibited *in vitro* by estrogen, progesterone, and deoxycorticosterone (Kalsner 1969). In the rat midbrain, COMT has been found to decrease during estrus (Salseduc et al. 1966).

In humans, several studies have investigated various peripheral measures of catecholamine metabolism during the menstrual cycle. Wiener and Elmadjian (1962), and Patkai et al. (1974) reported increases in urinary norepinephrine excretion during the premenstruum. A later study also measured urinary epinephrine excretion and found small nonsignificant decreases during the 5 days prior to menstruation. A more recent study (DeLeon-Jones et al. 1978) measured the urinary metabolite of central norepinephrine, 3-methoxy-4-hydroxyphenylglycol (MHPG), daily in four healthy women. A statistically significant increase in MHPG was found during the late luteal phase, followed by a rapid decline 2 days prior to menstruation, with a subsequent elevation during

the menses. This premenstrual drop in MHPG excretion is interesting in view of previous findings of decreased MHPG in some individuals with depressive illness (Beckman & Goodwin 1975).

During the premenstrual-menstrual phase of the cycle, sensitivity to tyramine increased, this probably being either a measure of increased noradrenergic receptor sensitivity or increased presynaptic neuronal norepinephrine activity (Chose & Turner 1977). In view of the above noted premenstrual decreases in urinary MHPG, it may be that sensitivity to tyramine is reflective of increased receptor sensitivity, complimenting decreased norepinephrine turnover and activity.

There are several lines of evidence, in addition to that described above, that would support an indoleamine role in premenstrual tension. Rats treated with a series of injections of progesterone showed increased brain serotonin uptake (Hackman et al. 1973) and turnover (Ladisich 1977) in several areas of the brain. After withdrawal of the progesterone injections, there was a decrease in brain serotonin uptake found 24 hours after withdrawal of the last progesterone injection (Hackman et al. 1973).

The uptake of serotonin into platelets has been found to be decreased in patients with depressive illness (Rausch et al. 1982), and decreases in platelet serotonin uptake have been found to occur in the premenstrual phase of the cycle (Rausch, unpublished; Taylor et al. 1981; Wirz-Justice & Chappius-Arntt 1976). The amino acid precursor of serotonin, tryptophan, has shown menstrual variations in the plasma, with increases seen premenstrually (Wirz-Justice et al. 1975).

The urinary metabolite of serotonin, 5-hydroxyindoleacetic acid (5-HIAA), has been measured across the menstrual period in normal women, and 5-HIAA excretion has been found to be higher during the secretory phase as compared to the proliferative phase, with the final descent occurring during the premenstrual phase (Lerdo de Tejada et al. 1978). This data could be consistent with the notion that luteal progesterone secretion increases serotonin turnover, with subsequent premenstrual progesterone withdrawal resulting in lowered serotonin turnover.

The serotonin hypothesis may bear some relevance to the mineralocorticoid hypothesis discussed above, since administration of the serotonin precursors tryptophan and 5-hydroxytryptophan have been found to stimulate renin in dogs, and stress can lead to increases in both plasma renin and brain serotonin (Check 1980). Furthermore, corticosterone itself can increase or decrease serotonergic function, depending on the dose (Aubert et al. 1971).

Acetylcholine Hypothesis

Some evidence exists that cholinergic mechanisms may be etiologic in the premenstrual-menstrual emotional upsets. Angiotensin increases brain acetylcholine content in rat and mouse and causes an increase in the output of acetylcholine from the parietal cortex of cats. It causes an increase in the secretion of antidiuretic hormone, which appears to be cholinergically mediated and itself is water retaining. Consistent with these observations, it has been noted that the uterine hyperemia which precedes menstruation is due to increased acetylcholine activity, and neostigmine, a cholinesterase inhibitor, can induce menstruation in nonpregnant women who have delayed menstruation, presumably by increasing uterine acetylcholine activity. Furthermore, a variety of ovarian hormones and other steroids can increase acetylcholine activity in physiologic preparations and can increase sensitivity to acetylcholine in muscle preparations.

Menstrually related remission of symptoms has been demonstrated in patients suffering from myasthenia gravis, and are asssociated with cyclic variations of red cell acetylcholinesterase activity, suggesting a hormonal influence on acetylcholinesterase activity (Vijayan et al. 1977). Physostigmine, a centrally acting cholinomimetic drug, alleviates manic symptoms and causes withdrawal, lethergy, dysphoria, psychomotor retardation and, in some cases, depression in normals, remitted patients, schizophrenics, and manics (Janowsky et al. 1972). Possibly, then, the premenstrual-menstrual emotional upsets in part represent a relative predominance of central cholinergic activity, caused by angiotensin or a variety of endogenous steroid compounds. Finally, there is some evidence that a proprietary combination drug containing an ergot, a barbiturate, and an anticholinergic agent can alleviate premenstrual tension better than placebo can (Robinson et al. 1977). If this finding is valid, and if the effects are due to the anticholinergic agent, this would support a role for acetylcholine in the ovarian-linked emotional disorders.

Summary

In the above paragraphs, the authors have reviewed several of the major hypotheses proposed to explain the etiology of premenstrual tension. Although there is evidence that premenstrual tension is linked to changes in hormones and/or neurotransmitters, the need for further research to confirm or refute the various hypotheses exists, and represents a challenge for the future.

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Psychopharmacology and the Anxiety Disorders Workshop

This special section of the *Psychopharmacology Bulletin* is devoted to proceedings at a workshop entitled, "Psychopharmacology and the Anxiety Disorders," held in Washington, D.C. on February 8-9, 1982. This was a relatively small meeting with 17 panelists and 15 guest scientists or staff from the National Institute of Mental Health. The workshop provided a forum for investigators to present their latest findings in this rapidly developing field and to try to resolve points of disagreement. There is now no question that psychoactive drugs, principally the antidepressants, are effective treatments for panic attacks and for obsessive-compulsive disorders. Evidence is also accumulating that the antidepressants are effective treatments for generalized anxiety disorders.

A major theme of the workshop was the possible mechanism(s) of action of the antidepressants as treatments for these disorders.

The articles that follow are expanded versions of papers presented at this workshop.

Allen Raskin, Ph.D., and
Jerome Levine, M.D.
Section Editors

Diagnostic Classification of Anxiety and Phobic Disorders

David V. Sheehan, M.B., B.Ch., B.A.O.[1] and Kathy H. Sheehan, M.S.[2]

[1]Hypnosis and Psychosomatic Medicine Clinic, Massachusetts General Hospital, Boston, MA 02116.
[2]Massachusetts General Hospital, Institute of Health Professions, Boston, MA 02116.

In order to understand and investigate anxiety disorders and correctly assign patients to treatment, it is helpful to have a diagnostic classification system. Such a diagnostic classification is like a map to a traveller: without it he may get quite lost, with it he is guided to any destination and his journey is eased considerably.

The multiaxial diagnostic system, recently introduced by Diagnostic and Statistical Manual-III (DSM-III), eliminates much of the confusion of past diagnostic systems. In this system each patient receives a diagnosis at five levels—one diagnosis for each axis.

Axis 1 - A diagnosis of the clinical psychiatric syndrome based on the clinical description of symptoms and signs.

Axis 2 - A personality disorder diagnosis based on the individual's character structure and mode of interaction with his environment.

Axis 3 - A diagnosis of medical (nonpsychiatric) disorder.

Axis 4 - Severity of psychosocial stressors.

Axis 5 - Highest levels of adaptive functioning in the past year.

This paper will focus on an Axis 1 diagnostic classification for anxiety disorders, i.e., the diagnosis of clinical psychiatric syndrome based on a description of the symptoms and signs. This is the preeminant, central axis to which the others are secondary.

Goals of Classification

The immediate goal of a classification system is to organize phenomena in a systematic way into categories in which members of each category have common characteristics, e.g., symptoms, signs, demography, pathophysiology, etiology, natural history, family history, and treatment

response. This is not intended as an obsessive academic exercise. The long-range purpose of having a good classification guide is to:

1) help predict what will happen to a patient who falls into one class based on the past experience with other patients in that class;

2) help control the symptoms by being able to predict and manipulate what will happen in several contingencies; and

3) clarify the relationship between the phenomena, e.g., the symptoms observed.

Classification is useful insofar as it helps to predict, clarify, and control what is going to happen.

Criteria for Classification

A good classification system satisfies the following criteria:

1) The classes are inherently mutually exclusive, i.e., each class is clearly distinct from the other classes; no class overlaps with another class;

2) the classes are internally homogenous, i.e., each class is internally consistent and homogenous within itself;

3) the classification system is comprehensive, i.e., it has a category for all cases;

4) it helps to clarify the relationship between the phenomena in question;

5) it permits better prediction and control; and

6) it is simple, economical, and clear.

The authors' comments will focus on the special importance of having classes that are inherently mutually exclusive and the proscription of significant category overlap. For if that first criterion is not satisfied, the classification system breaks down and the other criteria are meaningless.

Methods of Classification

There are many methods of setting up a classification system. The theological approach is to consult a consortium of experts and distill their collective wisdom. A more scientific approach involves two exploratory stages and a final testing or confirmatory stage. The first exploratory stage involves a cluster analysis of presenting symptoms in a large population to separate the symptoms into distinct groups. The second stage involves a discriminant analysis on these clusters to determine the symptoms (or criteria) with the highest discriminatory power between the clusters. These discriminating variables now become the diagnostic criteria for each class in the classification. The final confirmatory stage calls for a test of these new discriminating variables on a fresh patient population for their ability to a) comprehensively assign all cases into b) mutually exclusive groups.

The authors took the position that existing classification schemes for the anxiety disorders had completed the exploratory stages in arriving at the diagnostic criteria for each category. What remained was to test the existing classification systems to see how well their diagnostic criteria could comprehensively assign patients into mutually exclusive groups.

Table 1

Diagnostic Labels Synonymous with Endogenous Anxiety

	Atypical Depression
Anxiety Hysteria	Grand Hysterie
Hysteria (early descriptions)	Hysterical Neurosis
Globus Hystericus	Vertigo Hysterique
Anxiety Neurosis	Anxiety States (*Lancet*, 1952)
Anxiety Syndrome	Severe Mixed Neurosis
Pseudo Neurosis	Pseudoneurotic Schizophrenia
Borderline States (Klein, 1964)	Non-Specific Insecurity Fears
Locomotor Anxiety	Street Fear
Phobic Anxiety State	**Agoraphobia**
Phobic Anxiety Depersonalization Syndrome	Phobophobia
Separation Anxiety	Severe School Phobia
Effort Syndrome	Irritable Heart Syndrome
Da Costa's Syndrome	Neurocirculatory Asthenia
Cardiac Neurosis	Soldier's Heart
Hyperdynamic B Adrenergic Circulatory State	Autonomic Epilepsy
Nervous Tachycardia	Vasomotor Neurosis
	Vasoregulatory Asthenia
	Hypoglycemic Syndrome
Hyperventilation Syndrome	**Hypochondriacal Neurosis**
Panic Disorder	Depersonalization Neurosis
Autonomic Epilepsy	Depressive Anxiety States

Deficits in Existing Classifications of Anxiety Disorders

In one study, a list of diagnostic labels was collected from the past records of approximately 60 patients (Sheehan et al. 1980). All patients described the same set of symptoms. All had spontaneous panic attacks and all were polyphobic. The diagnostic labels had been given for the same set of symptoms, over a period of 20 years. Table 1 illustrates the range of diagnoses given to these patients. The diagnostic confusion reflected in this table suggested two possible explanations. One explanation reflected negatively on the diagnostic abilities of the evaluating psychiatrists. The second explanation was that the classification system for anxiety disorders was itself the source of the confusion. Obviously the second explanation was preferable, since it was more flattering to Boston psychiatrists. The list in Table 1 included many labels in DSM-II (1950) as well as others that had found historical favor with various groups.

In an effort to test the mutual exclusivity of existing diagnostic categories, symptom checklist, scale, and interview data were analyzed on 100 consecutive patients who sought treatment for anxiety attacks and multiple phobias at a Massachusetts General Hospital Psychiatry Clinic (Sheehan & Sheehan, in press-a,b,c). Because of the multitude of labels, it was necessary to choose for the testing phase only those for which there were precisely defined, replicable, diagnostic criteria and for which there was some consensual validation. The criteria of Feighner et al. (1972) and the Research and Diagnostic Criteria (RDC) (Spitzer et al. 1975) and DSM-III criteria (1980) satisfied this demand. The diagnostic criteria of Feighner et al. (1972) had three diagnostic labels which were relevant to this patient population: 1) hysteria 2) anxiety neurosis, and 3) phobic neurosis. Others including Perley and Guze (1962) had also proposed earlier variations of diagnostic criteria for hysteria. Table 2 shows the percentage of patients who satisfied the Feighner et al. diagnostic criteria for each diagnostic category. The majority of patients simultaneously fulfilled all of the criteria for a diagnosis of hysteria, and anxiety neurosis and phobic neurosis. As shown in Tables 3 and 4, they also satisfied the criteria for several RDC and

Table 2

(1) Percentage of Patients Having a Definite or Probable Diagnosis of Hysteria

Perley and Guze criteria	Feighner et al. criteria for hysteria	
	Including age of onset before 30	Exluding age of onset before 30
92%	71%	90%

(2) Percentage of Patients Having a Definite or Probable Diagnosis of Anxiety Neurosis

Feighner et al. criteria for anxiety neurosis	
Including age of onset before 40	Excluding age of onset before 40
95%	98% (84% "definite"-14% "probable")

(3) Percentage of Patients Having a Definite or Probable Diagnosis of Phobic Neurosis

Feighner et al. criteria for phobic neurosis (excluding Criterion 3 of Table 6)	
Including age of onset before 40	Excluding age of onset before 40
95%	100%

Table 3

Research Diagnostic Criteria and Other Symptom Clusters Simultaneously Satisfied by Sample

Diagnostic Category	Percent of Patients Satisfying Criteria
Panic Disorder	100
Generalized Anxiety Disorder	100
Phobic Disorder	100
Symptom cluster	
Obsessive Compulsive Symptoms	81
Hypochondriasis (Physical)	68
Hypochondriasis (Mental)	83
Dysphobic Mood "Atypical Depression"	92
Agoraphobic Syndrome (Marks 1969)	100
Polyphobic (as measured by Wolpe Lange FSS)	100

pages tightly bound

Table 4

DSM-III Categories Simultaneously Satisfied By Sample

Diagnostic Category	Percent of Patients Satisfying Criteria Excluding "Exclusionary Criteria"
Panic Disorder	100
Generalized Anxiety Disorder	100
Agoraphobia	100
Social Phobia	71
Simple Phobia	100
Obsessive-Compulsive Disorder	81
Conversion Disorder	100
Atypical Somatoform Disorder	100
Depersonalization Disorder	47
Hypochondriasis-Physical Health	68
Dysthymic Disorder	92

DSM-III categories simultaneously (DSM-III, 1980; Spitzer et al. 1975). This same sample of patients was found elsewhere to have a homogenous age of onset distribution, and a significant majority subsequently had satisfactory therapeutic responses to tricyclics and monoamine oxidase inhibitors (1980).

As indicated in Table 4, these figures were obtained when "exclusionary criteria" in the DSM-III were eliminated from the testing set of criteria. An exclusionary criterion is one that states that if a patient is given diagnosis X, he cannot also get diagnosis Y. An example from DSM-III (1980) is the last (exlusionary) criterion for panic disorder which states that such patients cannot have agoraphobia. It is by such charades that the pretense of mutually exclusive categories is maintained. However, there is no evidence in nature that having panic disorder confers an immunity against the development of agoraphobia. Indeed, quite the opposite seems to be the case. From this test on a fresh population it appears that these classification systems fail to satisfy the first criterion of a good classification—that of having categories that are mutually exclusive. Clearly there is considerable category overlap in these systems. The fable of the 10 blind men and the elephant may be relevant here. Each blind man holds a different part of the elephant and, in describing the part he holds, claims that it is the elephant. What is called for is a comprehensive overview and integration. If a patient seeks a physician's help stating he is anxious or describes some anxiety symptoms, there are 21 to 25 diagnostic categories in the DSM-III to which he might reasonably be assigned (*see* Table 5) (Sheehan & Sheehan, in press-a). Depending on the interest, or orientation of the diagnostician, any one or more of the patient's symptoms in the large cluster he suffers might be chosen and a diagnosis given around that cluster. Those with a medical model would favor panic disorder, while those with a behavioral orientation might select agoraphobia and social phobia.

Table 5

DSM-III Diagnoses Relating to Anxiety

Anxiety Symptoms	1. Panic Disorder
	2. Generalized Anxiety Disorder
	3. Atypical Anxiety Disorder
	4. Adjustment Disorder With Anxious Mood
Avoidance	5. Agoraphobia—With Panic Attacks
	6. Agoraphobia—Without Panic Attacks
	7. Social Phobia
	8. Simple Phobia
	9. Avoidant Personality Disorder
Physical Somatic Symptoms	10. Somatization Disorder
	11. Conversion Disorder
	12. Atypical Somatoform Disorder
	13. Depersonalization Disorder
	14. Hypochondriasis
	15. Histrionic Personality Disorder
Miscellaneous	16. Post-Traumatic Stress Disorder
	17. Obsessive-Compulsive Disorder
	18. Atypical Dissociative Disorder
Childhood	19. Separation Anxiety Disorder
	20. Avoidance Disorder of Childhood/Adolescence
	21. Overanxious Disorder
Possible	22. Factitious Disorder With Psychological Symptoms
	23. Factitious Disorder With Physical Symptoms
	24. Atypical Factitious Disorder With Physical Symptoms
	25. Malingering

Table 6

1 Panic Disorder	1		Possible Coexistence of DSM-III
2 Generalized Anxiety Disorder	– 2		
3 Atypical Anxiety Disorder	– – 3		Anxiety-Related Diagnoses
4 Adjustment Dis. With Anxious Mood	– – – 4		
5 Agoraphobia With Panic Attacks	– – – – 5		
6 Agoraphobia Without Panic Attacks	– + – – – 6		– = Combination Not Allowed
7 Social Phobia	+ + – – + + 7		+ = Combination Allowed
8 Simple Phobia	+ + – – + + + 8		138 Combinations Permitted
9 Avoidant Personality Disorder	+ + + – + + + + 9		
10 Somatization Disorder	+ – + – + + + + + 10		
11 Conversion Disorder	+ + + – + + + + + – 11		
12 Atypical Somatoform Disorder	+ + + – + + + + + – – 12		
13 Depersonalization Disorder	– – – – – – – – + + + + 13		
14 Hypochondriasis	– – + – + + + + + – + – + 14		
15 Histrionic Personality Disorder	+ + + – + + + + + + + + + + 15		
16 Post Traumatic Stress Disorder	+ + – – + + + + + + + + – – + 16		
17 Obsessive-Compulsive Disorder	– – – – – – + – + + + + – – + + 17		
18 Atypical Dissociative Disorder	+ + + – – + + + + + + + – + + + + 18		
19 Separation Anxiety Disorder	+ + – – + + + + + + + + – + + + + + 19		
20 Avoidance Dis. Of Childhood/Adol.	+ + – – + + + + – + + + – + + + + + + 20		
21 Overanxious Disorder	+ + – – – – – – – + + + – + + + – + – – 21		

As if it were not confusing enough to remember those 21 categories, the DSM-III recognizes that some of these categories could coexist. It therefore allows for the possible coexistence of some categories (1980). Table 6 outlines the relevant diagnostic categories that are permitted to coexist (+) and those that are not (–). This figure reveals that there are approximately 138 possible combinations of such diagnoses allowed by the DSM-III (1980). When a patient presents with a complaint of anxiety, the clinician has 138 combinations of diagnoses to consider. There may be more diagnostic combinations permitted than the patient has symptoms, a lucid example of misplaced precision. This makes useful comparison of studies from one center to the next difficult.

Case Illustration: Limits of a Cross-Sectional Perspective

Consider the following case of a patient admitted to the inpatient service at Massachusetts General Hospital, a patient whose entire cluster of symptoms responded well to phenelzine and behavior therapy (*see* Table 7) (Perly & Guze 1962;Spitzer et al. 1975).

Two years before admission the patient had attacks of unreality. At that point she fulfilled the criteria for a DSM-III diagnosis of depersonalization disorder (1980). One year prior to admission she became hypochondriacal about a few fleeting symptoms and sought much medical attention. At that point she fulfilled the DSM-III criteria for a diagnosis of hypochondriasis (1980). Six months prior to admission, the hyperactive episodes of autonomic manifestations of anxiety permitted the DSM-III label generalized anxiety disorder (1980). Three months prior to admission she choked on food while anxious and subsequently feared eating solid foods. This was sufficient to justify the label simple phobia, since this was now

Table 7

DSM-III Case Illustration

Time Before Treatment	DSM-III Diagnosis at Time
2 years	Depersonalization Disorder
1 year	Hypochondriasis
6 months	Generalized Anxiety Disorder
3 months	Simple Phobia
1 month	Social Phobia
6 days	Agoraphobia Without Panic Attacks
Admission	Conversion Disorder
1 week post-admission	Panic Disorder
2 weeks post-admission	Agoraphobia With Panic Attacks

her central concern. Her fears generalized so that before long she feared eating with her friends, going to restaurants, socializing at parties, being the focus of attention, eating with her family and, finally, even being seen eating by anyone. She preferred to eat alone. She had a social phobia. One week prior to admission she had a devastating panic attack while out driving and subsequently feared leaving her home. This was agoraphobia without panic attacks (she had not had three panic attacks over a 3-week period). With considerable effort, her family desensitized her to go out again. Their concern led to her being evaluated and admitted. On admission, the consultant described her central concern as preoccupation with choking sensations and a lump in her throat. This he diagnosed a conversion disorder (DSM-III) or what in the past would have been labeled globus hystericus. One week after admission she had a series of spontaneous panic attacks and now satisfied panic disorder criteria. Two weeks after admission, she was fearful of going anywhere. She could not leave the ward and even feared leaving the security of her room. She had agoraphobia with panic attacks (DSM-III) (1980).

Are we now to presume that this young lady had nine different diseases in the space of 2 years? If she had been seen cross sectionally at time period 3, would the authors have concluded she had generalized anxiety disorder and recommended a benzodiazepine? Or at time period 4, would a simple phobia have been described and behavior therapy and *in vivo* exposure been suggested? Or at time period 7, with a diagnosis of conversion disorder, might psychotherapy or hypnosis have been considered? At time period 8, the authors could comfortably recommend imipramine.

Clearly, a cross-sectional view can mislead. A more logical approach would be to view the case longitudinally as a process passing through several stages.

Stages of the Disorder: A Longitudinal Perspective

The majority of patients with this disorder may pass through the following seven stages in the natural progression of their illness (Sheehan & Sheehan, in press-c).

Stage 1 Subpanic Symptoms
Stage 2 Panic
Stage 3 Hypochondriasis
Stage 4 Single Phobia
Stage 5 Social Phobias
Stage 6 Agoraphobic Polyphobic Behavior
Stage 7 Depression

First, they usually suffer sudden episodes of isolated symptoms short of panic with little or no immediate stress, such as tachycardia, lightheadedness, or shortness of breath. These episodes may be followed by full-blown panic attacks which are more intense, and complete clusterings of several of these symptoms in the same time frame. Because there is frequently no apparent immediate stimulus for their physiology racing out of control, patients become hypochondriacal and repetitiously seek medical assistance. Over time, spontaneous panic attacks occur in increasingly varied situations. These spontaneous panic attacks can classically condition these situations to later elicit phobic anticipatory anxiety to these situations (induce single phobias). Over time, as the patients accumulated more phobias, they become more socially phobic and finally polyphobic and agoraphobic. Finally, as they become progressively restricted, and attempts at treatment fail, and they feel depressed and discouraged by their restrictions. All of these stages might be collapsed telescope fashion, into a short period of time. On the other hand, the progression may be protracted over many years or arrested at any one stage. It is the relentless onslaught of frequent, intense spontaneous panic attacks that dictates the rapidity and completeness of progression through the stages. (Sheehan & Sheehan, in press-a,c). This longitudinal perspective helps resolve the diagnostic confusion of many labels generated by the cross-sectional perspective (Sheehan & Sheehan, in press-a).

Toward a More Heuristic Classification

As a step towards a simpler, more practical classification system to guide research efforts and clinical management, a decision tree to another classification system is offered in Table 8 (Sheehan et al. 1981, Sheehan & Sheehan, in press-b,c). This classification proposes two kinds

of anxiety disorders. The presence or absence of spontaneous anxiety or symptom attacks that occur with little or no stress is the key differentiating point that triages a patient to one or other category (Sheehan et al. 1981; Sheehan & Sheehan, in press-b,c). The exogenous anxiety category is an anxiety that normal people can relate to. It occurs when someone is suitably traumatized or under stress or has a specific monophobia with anxiety that is exclusively bound to only one stimulus. The endogenous anxiety is associated with multiple symptoms, e.g., panic attacks, and eventually complicated by the acquisition of multiple phobias (Sheehan et al. 1981; Sheehan & Sheehan, in press-b,c). The exogenous category is stress-related, while the endogenous appears to be a genetically inherited metabolic disease (Sheehan et al. 1980, 1981). Both exogenous and endogenous anxiety can be subdivided into subtypes along acute to chronic and mild to severe/complicated continua (*see* Table 8) (Sheehan & Sheehan, in press-b,c). In the endogenous anxiety class, phobias usually occur. The presence of phobias in such patients appears to be a function of the intensity and frequency of the spontaneous panic attacks. The identity of the phobia appears to be a function of the situation in which intense panic attacks occurred. Subsequently, the phobias are reinforced both from within the individual by the spontaneous panic attacks and are triggered by a classically conditioned response to the environmental stimulus to which they have been conditioned (Sheehan & Sheehan, in press-c). Over time, the phobias are reinforced both from within and from outside the individual (Sheehan & Sheehan, in press-c).

Is there evidence to support such a clustering? There are data to suggest that the age of onset distribution, sex ratio, and treatment response are different in the two kinds of anxiety (Sheehan et al. 1980, 1981). In endogenous anxiety, the age of onset distribution is uniformly unimodal, consistent with a biological illness model. In exogenous anxiety, the age of onset is evenly distributed through all ages, consistent with a stress induction or conditioning model (Sheehan et al. 1981). Table 9 lists the diagnostic criteria for each major category, followed by the other suggested points of differentiation.

As long as classification systems depend exclusively on symptom clustering, it is unlikely that consensus will be reached among investigators. Consensus will probably await the development of laboratory techniques such as psychophysiological measures, blood or other laboratory tests, genetic marking, and pharmacological dissection. These will undoubtedly lend validity to some existing classification system and add refinements that will be clinically meaningful. In the meantime, the above analysis and classification system may offer investigators and clinicians a clearer starting point and easier guide to correct diagnosis and treatment.

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Table 8

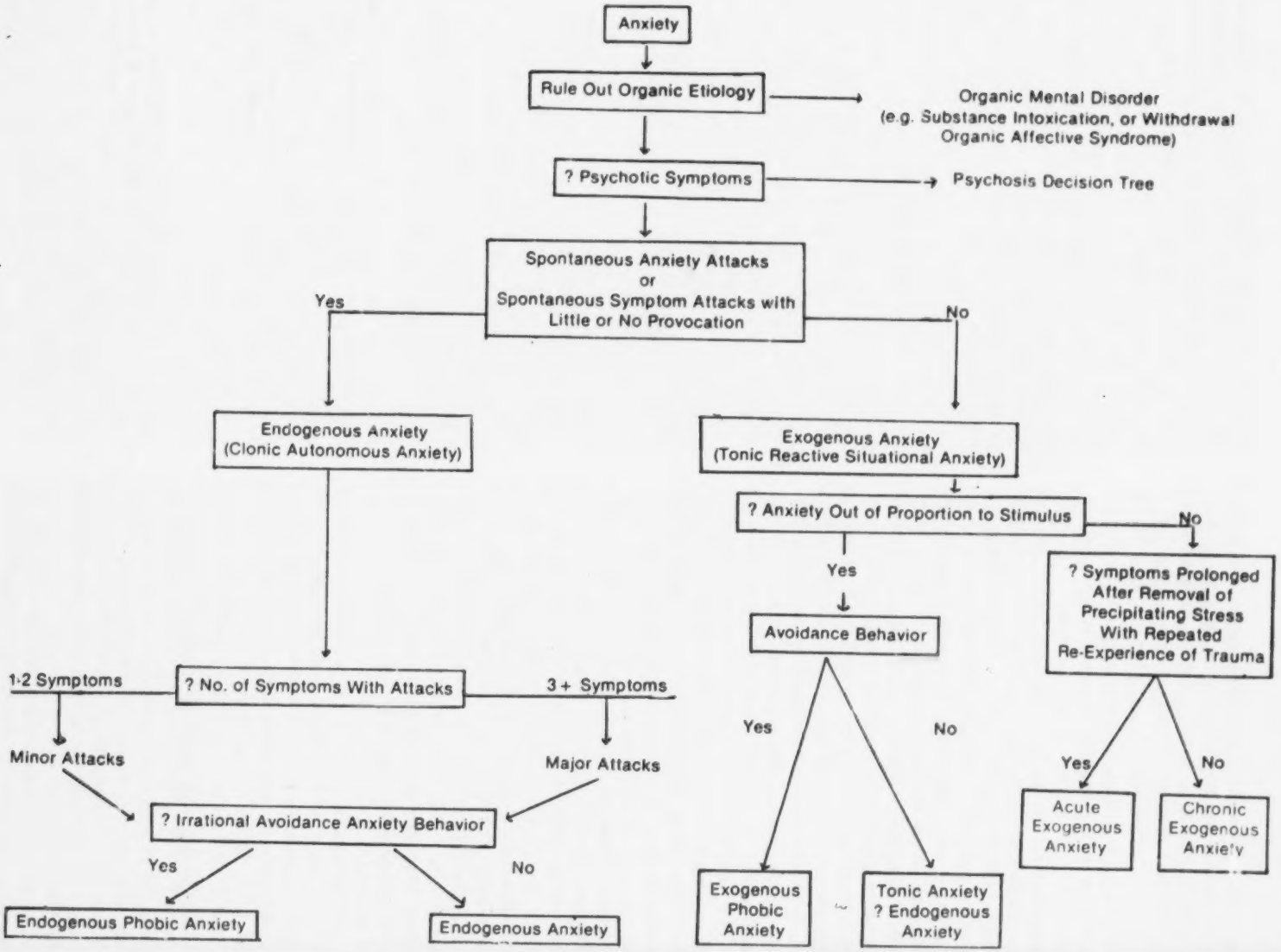
Anxiety
Rule Out Organic Etiology
Organic Mental Disorder
(e.g. Substance Intoxication, or Withdrawal
Organic Affective Syndrome)
? Psychotic Symptoms
Psychosis Decision Tree
Spontaneous Anxiety Attacks
or
Spontaneous Symptom Attacks with
Little or No Provocation
Yes
No
Endogenous Anxiety
(Clonic Autonomous Anxiety)
Exogenous Anxiety
(Tonic Reactive Situational Anxiety)
? Anxiety Out of Proportion to Stimulus
No
Yes
? Symptoms Prolonged
After Removal of
Precipitating Stress
With Repeated
Re-Experience of Trauma
Avoidance Behavior
1-2 Symptoms
? No. of Symptoms With Attacks
3+ Symptoms
Minor Attacks
Major Attacks
Yes
No
Yes
No
? Irrational Avoidance Anxiety Behavior
Acute
Exogenous
Anxiety
Chronic
Exogenous
Anxiety
Yes
No
Exogenous
Phobic
Anxiety
Tonic Anxiety
? Endogenous
Anxiety
Endogenous Phobic Anxiety
Endogenous Anxiety

Table 9

Diagnostic Criteria

Endogenous Anxiety	Exogenous Anxiety
1. Spontaneous, autonomous, clonic, phasic, (subjectively reported) episodes of the following symptoms: (1-2 for a minor attack, 3 or more together for a major attack): (a) Skipping or racing of heart (b) Dizzy spells or faintness (c) Air hunger, difficulty getting breath, or hyperventilation (d) Smothering or choking sensation (e) Tingling or numbness (paresthesias) in hands, arms, feet, or face (f) Nausea or upset stomach or vomiting (g) sudden unexpected panic or anxiety feelings occurring with little or no provocation (h) Hot flushes or cold chills (i) Jelly legs or imbalance (j) Shaking or trembling (k) Derealization or depersonalization (l) Chest pain, pressure or discomfort (m) Hypochondriasis (n) Feeling will lose control, scream or "go insane" or die (o) Spontaneous clonic alteration in sensory perception e.g. increased or decreased clonic sensitivity to light, sound, touch, temperature taste, proprioception, muscle power (p) Diarrhea attacks (q) Sweating episodes	1. No spontaneous panic or anxiety attacks or history of the same
2. Such symptom attacks have persistently recured for at least one month. Within a 3 month period, at least 3 discrete major attacks must occur for a diagnosis of major endogenous anxiety, or at least 3 discrete minor attacks for a diagnosis of minor endogenous anxiety. Symptoms must occur in the absence of any psychotic disorder or medical illness that could explain the symptoms.	2. Tension and symptoms of anxiety occur *only* in response to immediate, clearcut, = identifiable environmental stimuli. Onset of each attack not very sudden or unexpected but related to immediacy of triggering stimulus. In the case of conditioned changes in motor, sensory symptoms or special senses the symptom may occur alone without any overt anxiety.
3. Phobic symptoms particularly fear of a spontaneous panic attack (phobophobia) and fear of crowded places. Phobias start only after onset of first spontaneous panic attack. Phobia may fluctuate in intensity over time.	3. Phobia restricted to one specific focus. Monophobic rather than polyphobic. Phobia rarely fluctuates in intensity over time.
4. Depression, neurasthenia (excessive tiredness and feeling everything is an effort), obsessive compulsive symptoms present to some degree in over 2/3 of cases.	4. Depression, neurasthenia, obsessive-compulsive symptoms-and other gross psychophathology absent.
5. Anxiety profile of spontaneous panic attack as in Figure 1 (although Figure 2 type may also occur)	5. Profile of anxiety attack as in Figure 2
6. Spontaneous fluctuations on GSR	6. No spontaneous fluctuations on GSR
7. Slow habituation rate on GSR	7. Normal or rapid habituation on GSR
8. Elevated resting pulse rate	8. Resting pulse within normal range

Table 9 (Continued)

9. Brisk reflexes	9. Reflexes not hypertonic
10. Family history of anxiety attacks and phobic symptoms especially among female relatives	10. Positive family history rare
11. Age of onset usually 12-40 years	11. May occur at any age
12. 80 percent of cases occur in women	12. ?Equal sex distribution
13. More likely to have visited medical doctor and emergency ward several times for treatment of symptoms. Spontaneous anxiety must occur: 1. In absence of medical illness that could cause such symptoms 2. In absence of life-threatening situations	13. Rarely seeks medical or emergency ward treatment
14. More likely to have seen several psychiatrists in treatment over many years.	14.
15. More likely to have had a hospital admission and surgical treatment for symptoms.	15.
16. Response to MAO inhibitors and imipramine good	16. Response to drugs poor.
17. Response to behavior therapy alone poor.	17. Response to behavior therapy good
18. Autonomy of clonic phasic course e.g. does not immediately improve when environmental circumstances seem favorable.	18. More clearly responsive to psychosocial stimulus
19. Anxiety attacks precipitated by sodium lactate I.V. and by marijuana administration	19. Anxiety attacks not precipitated by either lactate or marijuana

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New Antianxiety Agents

Jonathan O. Cole, M.D.[1]

As stated by Greenblatt in his paper in this publication (p. 58), there is no real reason to expect that newer benzodiazepines (e.g., prazepam, halazepam) which are converted by the body into desmethyldiazepam will have antianxiety effects different from chlorazepate. Indeed, it is very hard to find differences even between less closely related benzodiazepines (BDPs) with quite different pharmacokinetics (e.g., diazepam and lorazepam). The possibility that one of the new triazolo-benzodiazepines, alprazolam, may have atypical efficacy in the treatment of panic states, as described by Sheehan (personal communication) and in depression (Feighner, in press) does suggest that further molecular changes in the BDP molecule *might* yield different or superior clinical actions.

There has been continuing interest in the use of older, marketed non-BDP drugs in anxiety. Propranolol has been suggested as especially useful in somatic or cardiac anxiety symptoms or in anxiety-related tremor. The available evidence only suggests a weak antianxiety effect of propranolol in anxious outpatients (Altesman et al. 1980). There are, of course, a growing number of newer beta-blocking drugs which might be studied for antianxiety effects, but it is hard to tell whether such studies would be productive.

The recently completed National Institute of Mental Health collaborative study comparing imipramine, chlordiazepoxide, and placebo in nondepressed anxious outpatients (Kahn et al. 1981) is showing that imipramine has unsuspected efficacy in anxiety. This effect comes on slowly, and some patients drop out because of imipramine's side effects. Other antidepressants deserve similar study. At least one new potential antidepressant, synaptamine, a mianserin analog, is being studied both in anxious and in depressed patients.

Another approach to the uncovering of new antianxiety drugs is the study in man of non-BDP substances which bind to BDP receptors. At least one such compound, CL 230, 482, a pyrazolo pyrimidine, is currently in early clinical trial in the United States. It is too early to tell whether this rational approach will yield an unfortunately rational result—the drugs may turn out to be exactly like existing BDPs in everything except chemical structure, reminding one of the "nonbarbiturate" hypnotics developed 30 years ago; these turned out to be at least as bad as the barbiturates in all respects, although chemically different.

The author is acquainted with one new antianxiety drug, buspirone, developed by Mead Johnson. It has been studied in anxious patients (Goldberg & Finnerty 1979; Rickels, in press) and has been shown to be as effective as diazepam. Recently it has been studied against diazepam and placebo in a large multiclinic study in anxious outpatients. These studies indicate that the drug is equipotent to diazepam with less sedation, good effect on anxiety, and some superiority over diazepam in reducing irritability and hostility as measured by the Symptom Check List (Newton, in press). Studies on the drug's abuse liability done in recreational sedative abusers at McLean Hospital are showing that at a higher dose (40 mg), buspirone is dysphoric although sedating and therefore unlikely to be abused (Cole et al. 1982).

All this is of some extra interest because buspirone has no effect on BDP receptors and has an odd mixture of dopamine agonist and antagon-

[1]Psychopharmacology Services, McLean Hospital, Belmont, MA 02178.

ist properties. It reverses neuroleptic-induced catalepsy in rodents both at low and at very high doses. It blocks the conditioned avoidance response without affecting escape, but also relieves conflict-induced behavioral suppression at doses similar to those at which diazepam has this "classic" antianxiety drug effect. Buspirone has neither neuroleptic nor BDP effects on social behavior in the rat, resembling low-dose piribedil, a presumed presynaptic dopamine agonist. It is much weaker at potentiating barbiturates than is diazepam. It is not anticonvulsant. In the cat, buspirone has effects on the quantitative electroencephalogram which resemble apomorphine. However, buspirone is an antiemetic. It does not produce physical dependence in rats (Riblet, in press).

Buspirone thus may be the first member of a quite different class of antianxiety drugs without the mild but bothersome abuse problems found with BDPs.

Hopefully, we are entering a new phase in the antianxiety area. For many years, the main and almost the only available drug group for treating depression was the tricyclic group, parallelling the BDPs in anxiety. Now a host of chemically and pharmacologically diverse antidepressants (e.g., trazodone, mianserin, zimelidine, nomifensine, buproprion) are available or in late clinical trial. Maybe buspirone will turn out to be effective and safe; maybe the new non-BDP drugs binding to BDP receptors will be usefully different; maybe some beta-blocker will be a first-class anxiolytic; maybe (quite likely) there are other new antianxiety drugs waiting in the wings unknown to us. One cannot be sure, but things seem to be looking up.

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Animal Models of Anxiety: Implications for Research in Humans

Thomas W. Uhde, M.D.,[1] Jean-Philippe Boulenger, M.D.,[1] Larry J. Siever, M.D.,[2] Robert L. DuPont, M.D.,[3] and Robert M. Post, M.D.[1]

In humans, behavioral and biological alterations may be associated with the subjective experience of anxiety (Krause 1961). However, no behavioral, biochemical, or neurophysiological correlates have been found to be specifically and consistently associated with the experience of anxiety. It is only by verbal report, therefore, that an observer can reliably detect the presence or absence of anxiety. In contrast, investigators using animal models must rely exclusively upon the behavioral and neurophysiological changes that develop in response to specific stimuli. Although it is impossible to develop specific criteria for anxiety in animals, there may be some useful parallels among the biological systems of nonhuman and human organisms.

Most animal models relevant to the topic of anxiety have been developed as systems for identifying drugs that may have anxiolytic properties in humans, rather than as attempts to induce a disorder in animals equivalent to the experience of anxiety in humans (Iversen 1979).

Models of Behavioral Inhibition

All of these models are based on the common principle that a number of different stimuli will induce a behavioral inhibition in animals (perhaps a consequence of fear) which can be antagonized by the administration of anxiolytic drugs (Gray 1981). The main purpose of these models is to differentiate the specific anxiolytic effect of the drug from sedation which would reinforce the behavioral inhibition (Simon & Soubrie 1979). The most commonly used of these models is the conflict test developed by Geller and Seifter (1960) in which the animals are conditioned to inhibit active food-seeking behavior in response to a signal of punishment. The barbiturates, meprobamate, and the benzodiazepines reinstate the suppressed behavior despite the occurrence of punishments, at doses which correlate well with their reported anxiolytic effects in humans (for review, *see* Sepinwall & Cook 1978). This so-called "anti-punishment" effect of anxiolytic drugs has been documented in several animal species (Dantzer 1977) as well as in humans (Carlton et al. 1981). However, no convincing results have been obtained on the conflict test with other substances such as morphine, ethanol, or beta-blockers, also known to have antianxiety effects (Sepinwall & Cook 1978).

These situations of conditioned fear, where a predictable and objectively unpleasant effect is expected, are different from those involving uncertainty, an emotion which may more closely approximate the human experience of generalized anxiety (File 1980). Uncertainty, triggered by a novel environment and/or different levels of illumination, has also been used in animal models to induce a decrease of exploratory behavior (Boissier et al. 1976; Crawley 1981) or social interactions (File 1980). Benzodiazepines also reverse the behavioral inhibition associated with these paradigms. It is interesting in this regard that agoraphobia may develop in some patients as a result of spontaneous panic attacks (Klein 1964, 1967) and that many patients restrict their life-

[1]Section on Psychobiology, Biological Psychiatry Branch, National Institute of Mental Health, Bethesda, MD 20205.
[2]Clinical Neuropharmacology Branch, National Institute of Mental Health, Bethesda, MD 20205.
[3]Phobia Program of Washington, Rockville, MD 20857.

Address reprint requests to: Dr. Thomas W. Uhde, Biological Psychiatry Branch, Room 3S-239, Building 10, National Institute of Mental Health, 9000 Rockville Pike, Bethesda, MD 20205.

style and avoid social interactions, presumably in response to the unpredictability of these attacks.

Separation Behavior in the Monkey

The use of the monkey may help to avoid some of the drawbacks encountered with the use of rodents, especially problems related to the interpretation of fear-associated behaviors. In rhesus monkeys, a forcible separation from an attachment object during rearing has been shown to induce a propensity in later life to exhibit behavior patterns typically associated with fear reactions but occurring in the absence of any obvious and immediate fear stimulus (Suomi 1981). The manner and the relative frequency with which these animals display symptoms characteristic of fear (perhaps similar to some types of anxiety experienced in humans) depends on the amount and type of stress encountered and on constitutional factors such as autonomic responsivity to auditory stimuli (Suomi 1981). The effects of antianxiety agents (benzodiazepines) on this model have not been investigated, although preliminary results suggest that imipramine not only inhibits the depressive symptomatology induced by separation, but decreases the amount of protest behavior displayed by young monkeys during separation (Suomi 1981). These findings are interesting in relation to the beneficial effects of imipramine described in some categories of pathological anxiety in humans, e.g., panic attacks and agoraphobia (Klein 1964; Uhlenhuth 1981).

It is also noteworthy that separation in primates has been used as a model of depression, suggesting some further parallelism with the human situation where both anxiety and depressive syndromes often occur simultaneously and respond to common treatments such as the tricyclic and monoamine oxidase inhibitor (MAOI) antidepressants.

Lack of response to escapable shock following exposure to inescapable shock or "learned helplessness" has likewise been conceptualized as a model of both depression and "anxiety-related" behavior; learned helplessness also responds to treatment with antidepressants (Anisman 1982; Maier & Seligman 1976; Seligman 1975). An interesting aspect of this model is its sensitization and conditioning characteristics; behavioral impairment increases with increasing numbers of exposures. This and related sensitization models may be particularly useful in the conceptualization of mechanisms underlying the at times progressive development of psychopathology observed in some clinical anxiety syndromes (Post & Ballenger 1981). Panic attacks and generalized anxiety may, in some instances, increase in frequency and severity leading to progressive incapacity of the patient. Models which take into account the longitudinal course of symptoms may be of particular value in conceptualizing mechanisms and therapeutic interactions which may differ greatly depending on when in the acute or chronic time course they are considered.

Kindling is another model which helps to focus on the longitudinal and progressive development of symptoms in addition to possible limbic system substrates, and the relationship of antianxiety and anticonvulsant effects of drugs such as the barbiturates and benzodiazepines (Post & Ballenger 1981; Post & Kopanda 1976). In kindling, animals show increasing behavioral electrophysiological and convulsive responses to repeated, intermittent stimulation. Limbic areas such as the amygdala and hippocampus are most susceptible to kindling (Goddard et al. 1969). Anxiety is one of the common effects reported in patients following spontaneous or induced seizures of the limbic system. It is of interest that selected drugs are both anxiolytic and potent anticonvulsants.

The Locus Coeruleus as a Model of Anxiety

Recent advances in research techniques provide unique opportunities for studying the behavioral consequences of both "turning-on" and "turning-off" specific brain systems. Although several neurotransmitters have been implicated in the biological functions of fear and arousal, the noradrenergic system may be especially interesting in this regard (Boulenger & Uhde 1982; Redmond & Huang 1979; Uhde et al. in press). In studes in the rhesus monkey, Redmond (1977) and Redmond and Huang (1979) investigated the behavioral effects of both increasing and decreasing the activity of the locus coeruleus, the major brain noradrenergic nucleus located in the pons with projections to the cerebral cortex, cerebellum, limbic system, and spinal cord. Redmond (1977) and Redmond and Huang (1979)

demonstrated that electrical and pharmacological activation of the locus coeruleus produced behaviors (e.g., eye scanning, head and body turning, scratching, biting fingers or nails, hand wringing, pulling hair) similar to those observed in monkeys exposed to natural threats in the wild. In contrast, electrical lesions and pharmacological inhibition of the locus coeruleus decreased these same fear-associated behaviors. For example, the microiontophoretic application of the alpha-2 adrenergic antagonists, yohimbine and piperoxane, simultaneously increased locus coeruleus firing and fear behaviors. Conversely, drugs which decrease locus coeruleus firing such as morphine, desmethylimipramine, MAOIs, and clonidine reduced fear-associated behaviors. These findings in the monkey may have interesting parallels in man. That is, drugs which increase locus coeruleus activity (piperoxane, yohimbine, methylxanthine) (Redmond 1977; Redmond & Huang 1979) or decrease it (morphine, desmethylimipramine, MAOIs, ethanol, diazepam) (Aghajanian 1978; Grant et al. 1980; Korf et al. 1974; Nyback et al. 1975; Redmond & Huang 1979; Strahlendorf & Strahlendorf 1981a,b) have been reported in humans to have anxiogenic and anxiolytic properties, respectively. Furthermore, propranolol, a beta-blocker with an anxiolytic profile in some humans also attenuates the postsynaptic effects of the norepinephrine released as a result of locus coeruleus activity (Redmond 1979). The relationship of locus coeruleus function to fear behaviors in the monkey, the potent inhibition of locus coeruleus activity by clonidine, and the fact that clonidine decreases both central and peripheral norepinephrine activity in man (Hanson & Hökfelt 1981; Leckman et al. 1980; Uhde, Siever, Post, and Jimerson, unpublished manuscript) led to the hypothesis that clonidine might have anxiolytic properties.

The Effects of Clonidine on Anxiety

Svensson et al. (1978) first reported in an open and uncontrolled study that clonidine had antianxiety properties in a group of patients with unspecified anxiety disorders. Uhde and coworkers (1980a) also found that clonidine dramatically decreased self- and nurse-rated items of anxiety in a group of nine opioid-addicted patients abruptly withdrawn from methadone. This antianxiety effect in addicted patients is noteworthy, since many symptoms of opiate withdrawal are similar to symptoms of severe anxiety. The authors' preliminary unpublished data also indicate that many panic-anxious patients obtain high ratings on the Addiction Research Center Inventory Subscale for Weak Opiate Withdrawal (ARCI) (Haertzen 1966), supporting the hypothesis that some aspects of opiate abstinence and panic anxiety may involve alterations of a common neurophysiological system.

As part of an ongoing anxiety research program at the National Institute of Mental Health (NIMH), intravenous clonidine (2μg/kg) and saline infusions were randomly administered under blind conditions to highly anxious depressed and agoraphobic patients (all had panic syndromes) and normal volunteers, in order to assess clonidine's effects on anxiety (Uhde et al. 1980, 1981, in press). As illustrated in Figure 1, the combined group of depressed and panic-phobic patients had significantly decreased ratings of anxiety following clonidine compared to baseline, but no change after placebo-saline infusions. The antianxiety and sedative effects were unrelated. Furthermore, neither clonidine nor placebo influenced baseline ratings of anxiety, as measured by the Spielberger State-Trait Anxiety Inventory in the normal volunteers. This lack of effect on anxiety in the authors' normal volunteers is consistent with the results of Leckman et al. (1980), although the normal subjects in both studies had low baseline ratings of anxiety before clonidine was administered. In another study, Liebowitz and colleagues (1981) administered open oral clonidine to 11 patients with panic disorder or agoraphobia with panic attacks. Four patients demonstrated a good antipanic response after a dose of 200–500 mcg daily. Four patients who initially improved with clonidine experienced a reduction in benefits with chronic administration, and three subjects (including one who reported less severe panic attacks) could not tolerate doses greater than 300 mcg daily. Hoehn-Saric et al. (1981) found clonidine superior to placebo in a double-blind treatment study of 23 patients with generalized anxiety or panic disorders. In the same study, clonidine was found to be as effective in the treatment of patients with generalized anxiety as those with panic attacks. These findings are noteworthy, since previous studies found that panic attacks are blocked by

tricyclic antidepressants (Klein 1964) and MAOI (Sheehan et al. 1980) but not by benzodiazepines (McNair & Kahn 1981) or neuroleptics (Klein 1967). More recently, Ko and associates (in press) at Yale found clonidine comparable to imipramine in reducing panic attacks and blocking panic symptoms in patients who were exposed to phobic stimuli which previously elicited panic attacks.

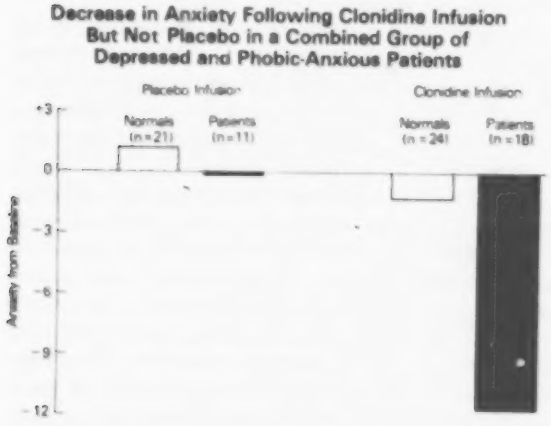

FIGURE 1. In a combined group of depressed ($N = 14$) and agoraphobic patients ($N = 4$), there was a significant decrease in ratings of subjective anxiety following clonidine compared to baseline. (Ten of fourteen depressed and four of four patients with agoraphobia experienced a reduction in anxiety as measured by the Spielberger State-Trait Inventory).

Preliminary data from the authors' double-blind crossover study at the NIMH (Uhde et al. in press) in five patients with panic disorder also suggest that ratings of generalized anxiety and panic attacks decreased after both the acute infusion and the first week of oral administration of clonidine. However, four of the five patients with panic disorder developed tolerance within 3 weeks of chronic clonidine administration (as illustrated in the single case in Figure 2). These findings are consistent with those reported by groups at Columbia (Liebowitz et al. 1981) and Johns Hopkins (Hoehn-Saric et al. 1981). Furthermore, the loss of anxiolytic effects with chronic treatment parallels the time course and development of tolerance to the inhibiting effects of clonidine on the firing rate of the locus coeruleus in animals (Engberg et al. 1982).

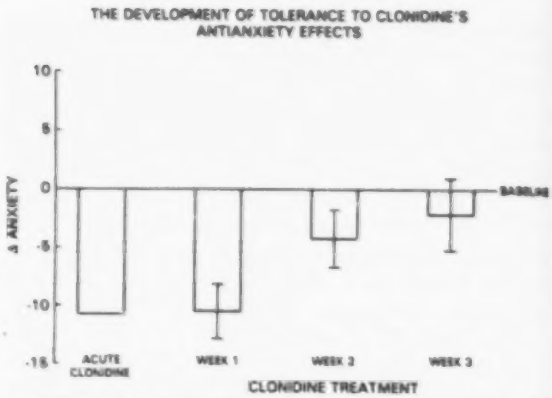

FIGURE 2. In a patient with panic disorder, clonidine treatment initially produced a decrease in self-rated items of anxiety comparable to that achieved by an acute intravenous challenge with clonidine. Ratings of state anxiety obtained during the third week of clonidine administration, however, are not significantly different from baseline-placebo scores, as measured by the Speilberger State-Trait Anxiety Inventory.

In addition to tolerance, clonidine treatment may be associated with a number of untoward side-effects such as drowsiness, sedation, and dry mouth (Hoehn-Saric et al. 1981; Liebowitz et al. 1981; Uhde et al. 1981). The role of the locus coeruleus in fear-related behaviors, arousal, and the sleep-waking cycle may explain the common association between anxiety reduction and sedation for most of the anxiolytic drugs, e.g., benzodiazepines, barbiturates, and meprobamate (Lader 1979).

The combined results of these studies suggest that clonidine may have noteworthy antianxiety effects in depressed, phobic, and panic-anxious patients, as well as patients undergoing opiate withdrawal. In addition, preliminary data suggest that independent measures of nonadrenergic activity may be related to clonidine's antianxiety properties (Ko et al. in press; Uhde et al. 1982, in press). Although clonidine may be less well tolerated by anxious patients than non-anxious hypertensive patients undergoing opiate withdrawal (Uhde et al. 1980a), double-blind comparisons of clonidine to standard drug treatments, e.g., imipramine, are indicated.

Discussion

Anxiety is a subjective experience unique to the

human organism. It is impossible to induce in animals a state which, in all its aspects, is equivalent to human anxiety. Nonetheless, animal models may have both practical and heuristic value. For example, the Geller-Seifter test is useful for identifying drugs with antianxiety effects in humans. The disadvantage of this test and other paradigms of behavioral inhibition is that not all drugs with antianxiety (e.g., morphine) or anti-panic (e.g., imipramine) effects in man have anti-punishment effects in animals.

The fear behaviors associated with locus coeruleus function would appear to be a new model relevant for identifying drugs with not only anxiolytic (agents which decrease firing of the locus coeruleus) but also anxiogenic (agents which increase firing of the locus coeruleus) properties. On the basis of its inhibitory effects of the locus coeruleus, clonidine was predicted to have at least transient antianxiety effects in humans (Redmond 1979). Preliminary results would appear to support this hypothesis, since clonidine subsequently has been found to have anxiolytic properties in patients with endogenous anxiety disorders (Hoehn-Saric et al. 1982; Liebowitz et al. 1981; Uhde et al. 1982), depression (Siever et al. 1981; Uhde et al., 1981), and in patients undergoing opiate withdrawal (Uhde et al. 1980a). The noradrenergic locus coeruleus as a functional unit also may be useful as a model for conceptualizing how a single neurotransmitter system might influence opposite emotions on a continuum from "fearlessness" to "panic."

The most problematic aspect of any animal model of human psychopathology is that human emotion is influenced by an intricate and elaborate process of interpretation. That is, human emotion (anxiety) may depend, in part, on the "meaning" of a given stimulus or situation. On the basis of past experience and learning, the biological systems of animals may also be influenced by the "meaning" of a stimulus. The investigations of Segal and Bloom (1976a,b) involving the stimulation of the locus coeruleus during simultaneous recordings from hippocampal neurons may be relevant to this topic. The noradrenergic nucleus locus coeruleus may influence, among other systems, the function of the limbic system, a neuroanatomical substrate which also has been implicated in the modulation of anxiety, mood, and behavior. The locus coeruleus, therefore, may have some capacity for potentiating both inhibitory and excitatory responses which, in turn, may be differentially coded in the same neuron, depending on the relevance of that stimulation to the organism based on prior experience and learning.

Thus, despite the inadequacies of animal models, they may be of both practical clinical value in the development of new drugs and also of heuristic value in conceptualizing possible underlying mechanisms of human anxiety.

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Caffeine Consumption and Anxiety: Preliminary Results of a Survey Comparing Patients with Anxiety Disorders and Normal Controls

Jean-Philippe Boulenger, M.D., and Thomas W. Uhde, M.D.[1]

Caffeine, a potent stimulant of the central nervous system (Rall 1980), is widely consumed in America where its estimated daily intake is approximately 200 mg per adult (Gilbert 1976). Symptoms of caffeinism, which are similar to those of anxiety, may develop in individuals who consume more than 500 mg of caffeine daily (Greden 1974). Furthermore, a significant association between caffeine consumption and self-ratings of trait-anxiety and depression has been demonstrated in a group of randomly selected students (Gilliland & Andress 1981). In psychiatric patients, similar results have been reported; i.e., high caffeine consumption was significantly associated with high scores of state-anxiety (Winstead 1976), depression, and both state- and trait-anxiety (Greden et al. 1978). In these studies, however, diagnostic subgroups were not taken into account, a factor which may influence caffeine-related symptomatology both qualitatively and quantitatively. Furthermore, the relationship between caffeine consumption and the incidence of psychopathological symptoms has never been studied in comparison with a control group, a methodological precaution that may be of importance since numerous factors, e.g., age and sex, may influence these two variable (Gilbert 1976; Sartorius 1980).

The authors therefore undertook a survey to study both caffeine consumption and the incidence of various symptoms in patients with anxiety disorders and major affective disorders that fulfilled the Research Diagnostic Criteria (RDC) (Spitzer et al. 1978). These data were compared with those obtained from a group of normal volunteers matched for age and sex. In this paper, as part of this ongoing research, preliminary results obtained in 16 anxious patients and 16 normal controls are presented.

Method

Sixteen anxious patients (15 females, 1 male) with a mean age of 41.2 ± 9.4 years (mean ± S.D.) and 16 age-matched (40.2 ± 10.2 years) and sex-matched controls without significant history of psychiatric illness, were invited to participate in this study. Fourteen patients had both panic and phobic disorders and two patients had both generalized anxiety and phobic disorders according to the RDC. Two patients with symptomatology consistent with a diagnosis of panic disorder were excluded because of concomitant medical illnesses. The 16 normal controls were recruited from the patients' relatives and friends in order to control for sociocultural variables.

Each subject completed a self-rating questionnaire (which may be obtained by writing to the authors), designed by the investigators to assess the consumption of various caffeinated beverages, foods, or drugs and the effects of caffeine on various somatic and psychological symptoms. The consumption of tobacco and medications (including over-the-counter medications) taken more often than twice-monthly was also recorded. The daily caffeine intake was calculated from this questionnaire according to the quantities of caffeine suggested by Gilbert (1976) for different

[1]Section on Psychobiology, Biological Psychiatry Branch, National Institute of Mental Health, Bethesda, MD 20205.

Address reprint requests to: Thomas W. Uhde, M.D., Biological Psychiatry Branch, Building 10, Room 3S-239, National Institute of Mental Health, 9000 Rockville Pike, Bethesda, MD 20205.

beverages, i.e., dripped coffee: 110 mg/cup; percolated coffee: 75 mg/cup; instant coffee: 65 mg/cup; decaffeinated coffee: 2 mg/cup; tea: 30 mg/cup; cola drinks: 40 mg/12 oz.; cocoa: 20 mg/cup. The caffeine intake related to drugs or chocolate bars (20 mg/bar) was added to the previous total.

In addition, the Spielberger State-Trait Anxiety Inventory (STAI) (Spielberger et al. 1970) and the Hopkins Symptom Checklist (HSCL-90) (Derogatis et al. 1976) were administered. The following subscales were derived from the HSCL-90 items: General Symptomatic Index (GSI), Positive Symptom Distress Index (PSDI), anxiety and phobic factors (Derogatis et al. 1976), phobic-anxiety, agitated depression, retarded depression, interpersonal sensitivity, somatization, obsessive-compulsive, and anger-hostility factors (Lipman et al. 1979).

Results

Daily Caffeine Consumption

The anxious patients consumed 185.9 ± 157.9 mg/day (mean ± S.D.) of caffeine, whereas the normal controls consumed 216.2 ± 174.9 mg/day (*t*-test, N.S.). There was no relationship between daily caffeine consumption and age, smoking habits, drug, or psychiatric treatments. Of all the individuals who no longer drank coffee, a significantly greater number of anxious patients (7 of 9) reported doing so because of the induction of anxiety, tension, and/or nervousness compared to the normal controls (2 of 5) (chi-square, $p < 0.05$). With the exception of one patient with panic disorder, all subjects were still consuming significant amounts of other caffeinated beverages.

State- and Trait-Anxiety

As expected, the anxious patients had significantly higher ratings of state-anxiety (50.19 ± 10.26) and trait-anxiety (54.14 ± 10.85) compared to the normal controls (state = 32.09 ± 4.21, $p < 0.001$; trait = 33.36 ± 5.18, $p < 0.0001$). Furthermore, in the anxious patients there was a significant positive correlation between daily caffeine consumption and trait-anxiety ($r = 0.90$; $p = 0.0001$) but not state-anxiety ($r = 0.007$; N.S.) (*see* Figure 1)

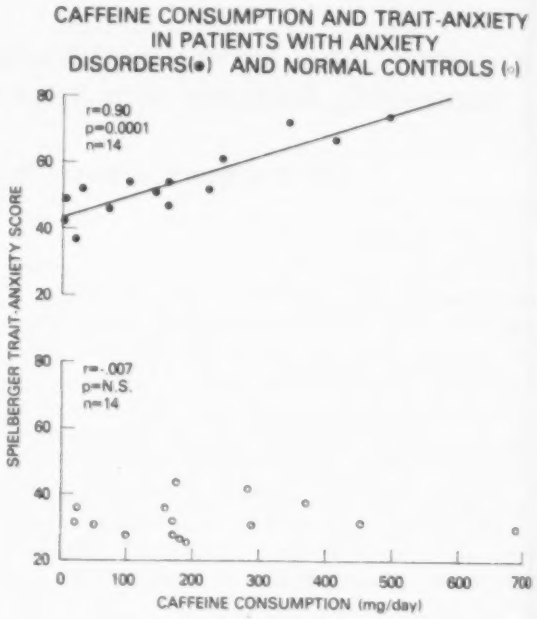
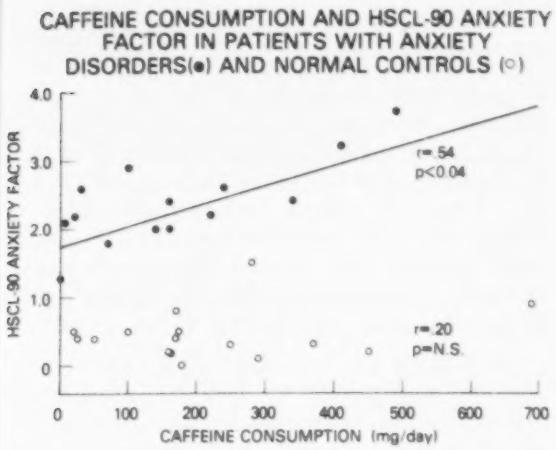


FIGURE 1

Subscales Derived From the HSCL-90

As expected, the anxious patients had significantly higher scores on the various subscales of the HSCL-90 compared to the normal controls, as indicated by the GSI (patients 1.55 ± 0.69; controls 0.38 ± 0.36; *t*-test $p < 0.0001$) and the PSDI (patients 2.31 ± 0.51; controls 1.43 ± 0.34; *t*-test $p = 0.0001$) indices. There was no relationship between caffeine consumption and the HSCL-90 subscales in the control group. However, in the anxious patients there was a significant positive relationship between caffeine consumption and the following subscales: retarded depression ($r = 0.80$; $p = 0.0003$; GSI ($r = 0.77$; $p = 0.0005$); obsessive-compulsive ($r = 0.74$; $p = 0.002$); hostility ($r = 0.72$; $p = 0.002$); somatization ($r = 0.68$; $p = 0.005$); PSDI ($r = 0.68$; $p = 0.006$); interpersonal sensitivity ($r = 0.61$; $p = 0.016$); agitated depression ($r = 0.53$; $p = 0.043$). Furthermore, it is noteworthy that in



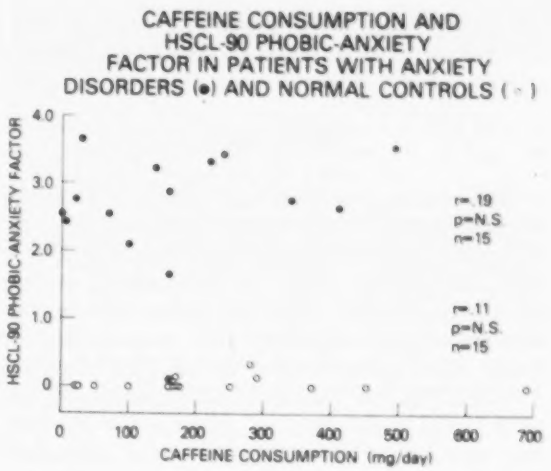


FIGURE 2

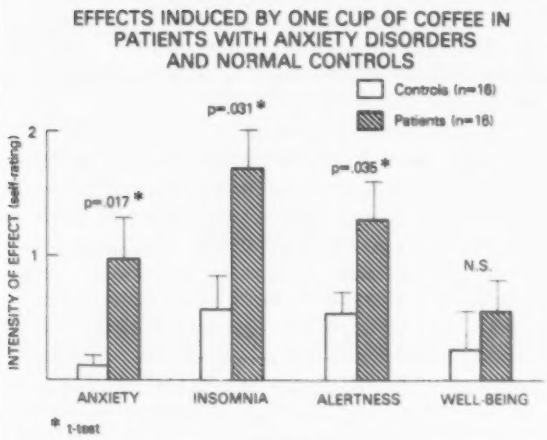


FIGURE 3

the anxious patients there was a significant positive correlation between caffeine consumption and those factors which primarily reflect generalized anxiety (anxiety: $r = 0.54$; $p = 0.038$) but not those which primarily reflect agoraphobia (phobic-anxiety: $r = 0.19$; N.S.) (*see* Figures 2a and 2b).

Caffeine Effects on Various Psychological and Somatic Symptoms

All subjects were asked to rate changes, if there were any, in their anxiety, alertness, sleep, and mood induced by drinking one cup of coffee, on a 4-item scale. As illustrated in Figure 3, the consumption of even one cup of coffee was associated with more intense ratings of anxiety, insomnia, and alertness in the anxious patients compared to normal volunteers.

Because anxiety and insomnia may be present at baseline before any coffee consumption, subjects were asked to indicate whether coffee induced or increased symptoms already present. Among those for whom coffee induced symptoms, i.e., those having a baseline level equal to zero, the caffeine-induced effects were greater in the patients compared to the normal controls, although this effect was nonsignificant.

All subjects were also asked to check, on a list of 26 symptoms, those items they associated with the consumption of coffee and to rate their intensity on a 5-point scale (0-4). For the anxious patients the caffeine-induced symptoms reported to have a mean score > 1 were, by order of decreasing intensity (mean $\pm$ S.D.): tension, nervousness (1.87 ± 1.36); anxiety (1.69 ± 1.49); insomnia (1.69 ± 1.70); increased urination (1.27 ± 1.53); increased motor activity (1.12 ± 1.36); tremors (1.12 ± 1.59); diarrhea (1.00 ± 1.51). For the normal controls, these caffeine-induced symptoms were: insomnia (1.31 ± 1.30) and increased motor activity (1.19 ± 1.28). The intensity of the following caffeine-induced symptoms was significantly higher in the patient group (t-tests): anxiety ($p = 0.004$); tremors ($p = 0.016$); muscle ten-

sion ($p = 0.028$); panic attacks ($p = 0.041$); lightheadedness ($p = 0.044$); diarrhea ($p = 0.046$).

Discussion

The present investigation is the first to survey the consumption and effects of caffeine in a group of patients suffering from phobic disorders associated with either panic or generalized anxiety symptoms. In this group the daily caffeine consumption (185 mg/day) was nonsignificantly lower than in a control group (215 mg/day) matched for age and sex. A similar result had been found by Greden et al. (1981) when comparing the caffeine consumption of hospitalized psychiatric patients to that of hospitalized nonpsychiatric patients. In the present study the caffeine consumption found in both groups was similar to the average daily consumption in American adults reported by Gilbert (1976), i.e., 200 mg/day.

A major finding of this study was that a highly significant positive correlation ($r = 0.90$; $p < 0.0001$) existed between the daily caffeine consumption and the scores of trait-anxiety within the patient group but not in the control group (Figure 1). Such a correlation would not appear to be related to the consumption of benzodiazepines by the patients even though caffeine has been shown to antagonize the biochemical (Boulenger et al. 1982) and pharmacological (File et al. 1982) effects of benzodiazepines in humans. Only five patients who were caffeine users (10-240 mg/day) were also taking psychotropic drugs (all being minor tranquilizers). Thus, our preliminary results suggest that an increased sensitivity to the effects of caffeine may exist in anxious patients as composed to normal controls, a finding similar to that described for other compounds, e.g., lactate, epinephrine, or isoproterenol (for review, *see* Pitts & Allen 1979). This increased sensitivity would explain in part why significantly more anxious patients than controls have given up coffee because of its central nervous system stimulant properties, and why the caffeine-induced effects appear to be significantly more severe in the former than in the latter (Figure 3). It is also possible that the higher baseline levels of anxiety and/or insomnia of the anxious patients may have contributed to these results. Double-blind, caffeine-placebo challenges are indicated in order to determine whether anxious patients are truly more susceptible to caffeine-related anxiety symptoms than controls.

In contrast to trait-anxiety, state-anxiety was not related to caffeine consumption in either the anxious patients or the normal controls. Such a result may not be surprising since it is more likely that habits of caffeine consumption might be related to trait-anxiety (presumably a stable characteristic) rather than to state-anxiety (anxiety which fluctuates and reflects situational factors at the time of testing) (Spielberger et al. 1970).

Despite the use of similar rating scales (STAI), previous studies have reported conflicting results concerning the relationship between caffeine consumption and state- and trait-anxiety. While in normal students high caffeine consumption is asssociated with trait-anxiety but not state-anxiety (Gilliland & Allen 1981), studies of unspecified psychiatric inpatients have reported an association with state-anxiety alone (Winstead 1976) or both state- and trait-anxiety (Greden et al. 1978).

In addition to trait-anxiety, several HSCL-90 subscales were found to be significantly and positively correlated with caffeine consumption in the patient group but not in the controls. Such an association may be related to the increase of trait-anxiety found with increasing caffeine consumption or to a nonspecific and more generalized increase in the level of psychopathology. Other studies demonstrating a significant correlation between caffeine consumption and both anxiety and depression (Gilliland & Andress 1981; Greden et al. 1977) have also raised this problem. The extension of the present survey to include a group of patients with affective disorders should clarify the possible relationship between caffeine consumption and other types of psychiatric disorders.

Another interesting finding is the relationship between caffeine consumption and the scores of the HSCL-90 "anxiety" factor but not the "phobic-anxiety" factor (Figure 2). The "anxiety" factor, reflecting mainly generalized anxiety symptoms appears to be sensitive to caffeine effects in a dose-related manner while the "phobic-anxiety factor," reflecting mainly agoraphobic symptoms, is not significantly affected by caffeine consumption. These data are consistent with the description by Klein (1980) of agoraphobia as a distinct clinical entity with different clinical characteristics, symp-

toms, evolution, and pharmacologic response to antidepressant treatments.

In conclusion, the present study suggests that caffeine consumption is positively correlated with trait-anxiety in patients with phobic disorders associated with either panic or generalized anxiety disorders. Such a correlation may be related to an increased sensitivity of these patients to the effects of caffeine, particularly those symptoms related to generalized anxiety. In contrast, symptoms of agoraphobia do not appear to be influenced by caffeine consumption, a finding which supports its description as a distinct clinical entity. The correlation between the amount of caffeine consumed and other psychopathological factors such as depression raises the problem of the specificity of caffeine's effects on psychiatric disorders. Further surveys, including the use of caffeine challenge paradigms in various psychiatric patients, should help to clarify these relationships.

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New Anxiolytics: Are They Really New?[1]

David J. Greenblatt, M.D.,[2] and Richard I. Shader, M.D.[2]

The pharmaceutical industry continues its search for more specific and more effective pharmacologic treatments of anxiety. With a few recent exceptions (Rickels 1981), the great majority of new anxiolytics are of the benzodiazepine category. Benzodiazepines as a class of compounds clearly have increased the overall efficacy of anxiolytic pharmacotherapy relative to drugs available prior to 1960, and also have greatly increased the safety of such treatment. However, numerous benzodiazepines are clinically available as anxiolytics, and although superior as a class of drugs, meaningful differences among various drugs within the class are at best subtle. It is of great importance to pharmacologists, practicing physicians, and members of institutional formulary committees that clinical and pharmacokinetic characteristics of new benzodiazepine anxiolytics be carefully and critically evaluated before promotional claims of newness or uniqueness are accepted as valid. This paper briefly considers the properties of several new benzodiazepine anxiolytics, together with an assessment of their potential role in the pharmacotherapy of anxiety.

Halazepam and the Parade of Desmethyldiazepam Precursors

Halazepam (Paxipam) was recently introduced as a benzodiazepine anxiolytic in the United States (Figure 1). Clinical trials hav demonstrated its comparability to other standar benzodiazepine antianxiety agents, both in term of efficacy and side effects (Rickels et al. 197 Fann et al. 1982). The pharmacokinetic profile halazepam, however, reveals interesting prope ties. Many benzodiazepines are precursors desmethyldiazepam, being partly or completel transformed to this metabolic product (Figure 2) Two benzodiazepines already available in th United States—clorazepate and prazepam—ar in fact, nearly completely transformed desmethyldiazepam prior to reaching the systemi circulation (Allen et al. 1980; Shader et al. 198 Greenblatt et al. 1981a). Current data o halazepam appears to put this drug in a simila category. After a single oral dose of halazepam the intact drug appears in systemic blood onl transiently and at relatively low levels, bein rapidly transformed to the principal metaboli desmethyldiazepam (Figure 3). Due to its ver long elimination half-life (Allen et al. 198 Greenblatt et al. 1981a; Shader et al. 198 desmethyldiazepam persists in blood much longe than halazepam. During multiple-dose therap with halazepam, the parent drug will accumula minimally, whereas the major metabolite will a cumulate extensively, consistent with its very lon elimination half-life.

Since halazepam serves mainly as anothe precursor of desmethyldiazepam, it is difficult conclude that this drug would add meaningfu to the already available armamentarium of lon half-life accumulating benzodiazepines such diazepam, clorazepate, or flurazepam (Gree blatt et al. 1981a). Thus, halazepam serves as a example of a drug for which careful pha macokinetic studies can readily establish its likel role in clinical practice.

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[2]Division of Clinical Pharmacology, Department of Psychiatry, Tufts-New England Medical Center, Boston, MA 02111.

Address correspondence to: David J. Greenblatt, M.D., Division of Clinical Pharmacology, Box 1007, New England Medical Center Hospital, 171 Harrison Avenue, Boston, MA 02111.

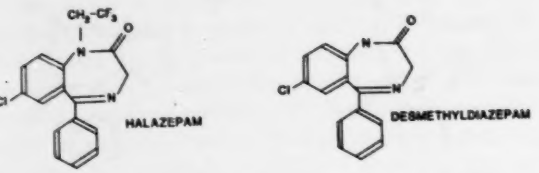


FIGURE 1. Structural formula of halazepam and its major metabolite, desmethyldiazepam.

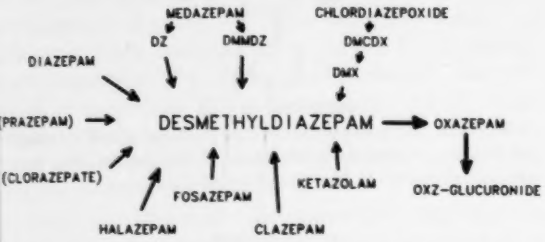


FIGURE 2. Schematic representation of the many benzodiazepines that are biotransformed to desmethyldiazepam.

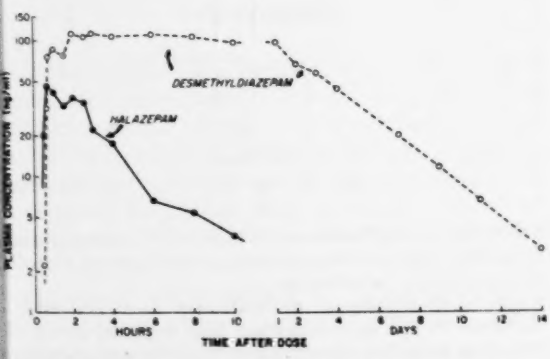
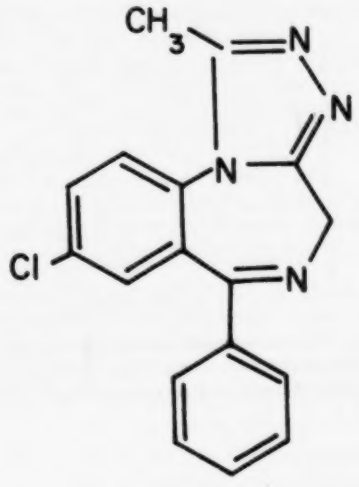


FIGURE 3. Plasma concentrations of halazepam and its major metabolite, desmethyldiazepam, in a volunteer who ingested a single 40-mg oral dose of halazepam.

Alprazolam: The Tirazolo Benzodiazepines

Another important research strategy for the development and evaluation of new benzodiazepines involves compounds whose structure deviates from the familiar 1,4-benzodiazepine configuration. The most important of these compounds is alprazolam, in which a triazolo ring is affixed to the positions previously designated as 1 and 2 (Figure 4). In clinical studies of anxiolytic efficacy in patients with neurotic anxiety, alprazolam performs similarly to other comparison benzodiazepines (Cohn 1981). An apparently unique property of this compound has been suggested by studies comparing its clinical efficacy to that of tricyclic antidepressants in patients with endogenous depression (Fabre & McLendon 1980). The results available to date suggest that alprazolam may have antidepressant as well as anxiolytic effects. If such findings are replicated in subsequent trials, this would be a unique and important property, since alprazolam has a relatively benign benzodiazepine-like profile of side effects as opposed to the more important and potentially serious side effect profile of the tricyclic antidepressants. Consistent with these reports are other preliminary findings suggesting that alprazolam may have efficacy in the treatment of panic attacks and related disorders.



ALPRAZOLAM

FIGURE 4. Structural formula of alprazolam.

None of these apparently unique clinical properties of alprazolam could have been predicted based on its pharmacokinetic profile (Greenblatt et al. 1982a). The metabolic disposition of alprazolam involves hepatic oxidation, yielding hydroxylated metabolites which reach the

systemic circulation in negligible quantities. Therefore, essentially all of the clinical activity of alprazolam is attributable to the parent compound. The apparent elimination half-life of alprazolam in humans usually ranges from 8 to 16 hours (Figure 5). As in the case of other benzodiazepines transformed by oxidation (Greenblatt et al. 1982b), the half-life is prolonged in elderly as opposed to young males due to reduced oxidizing capacity in the elderly male population.

In mechanistic terms, it has not established why alprazolam should have antidepressant as well as anxiolytic properties. It may well be that other triazolo benzodiazepines such as triazolam or estazolam share similar properties.

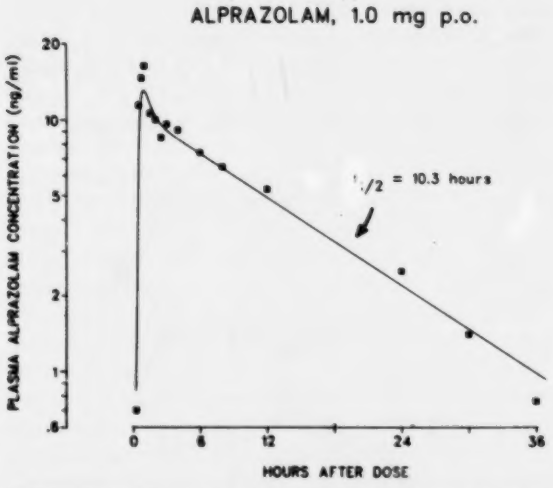


FIGURE 5. Plasma concentrations of alprazolam in a volunteer who ingested a single 1-mg oral dose. Solid line is the computer-determined pharmacokinetic function of best fit.

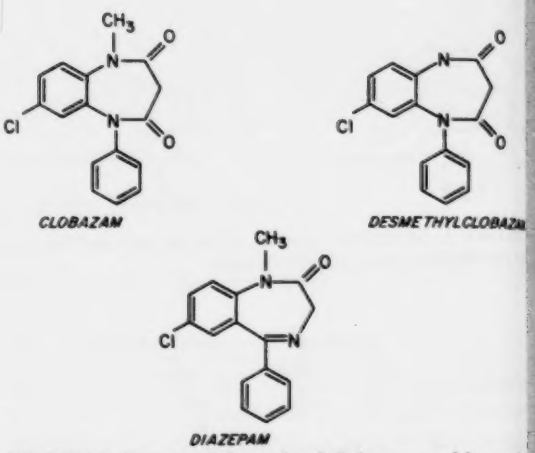


FIGURE 6. Structural formula of clobazam and its maj metabolite, desmethylclobazam. Also shown for com parison purposes is the structure of diazepam.

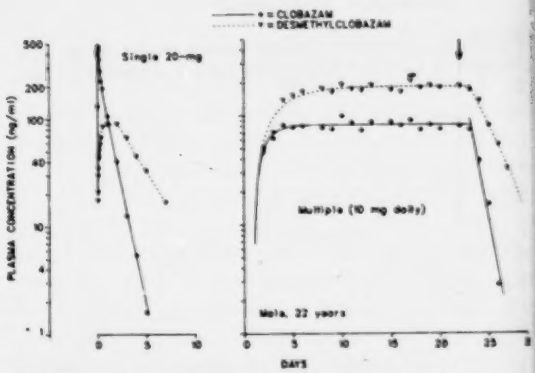


FIGURE 7. Left: Plasma concentrations of clobazam an desmethylclobazam in a volunteer who ingested a sing 20-mg oral dose of clobazam.
Right: Concentrations of clobazam and desmethy diazepam in the same volunteer who ingested 10 mg clobazam once daily for 22 days. Note the pattern of a cumulation as well as washout for both compounds aft the last dose (arrow).

Clobazam: A Shift of the Nitrogen

Clobazam is a 1,5-benzodiazepine derivative, and thereby differs from other benzodiazepines in the position of the nitrogen substituents on the central nucleus (Figure 6). Its anxiolytic efficacy has been clearly established in many controlled trials, and the drug is extensively used as an antianxiety agent in Europe (Brogden et al. 1980).

Despite the different positioning of the nitroge atoms, the metabolic profile of clobazam i humans closely resembles that of diazepam Biotransformation of clobazam proceeds b hepatic N-demethylation, yielding the pha macologically active metabolite, desmethy clobazam (Greenblatt et al. 1981b; Tedeschi et a 1981). This is entirely analogous to the situatio with diazepam, which is transformed to the activ substance desmethyldiazepam. For both

clobazam and diazepam, the elimination half-life of the metabolite is greater than that of the parent drug, and the clearance of the metabolic product is lower than that of the parent drug. For this reason, concentrations of desmethylclobazam after single oral doses of the parent drug persist in plasma considerably longer than those of clobazam (Figure 7). During multiple-dose therapy, accumulation of clobazam and desmethylclobazam is extensive, with levels of the metabolite generally exceeding those of the parent compound (Figure 7). After discontinuation of therapy, both compounds wash out from plasma at a slow rate, although desmethylclobazam persists longer than the parent drug. All of these characteristics are highly analogous to the situation seen during single and multiple dosing with diazepam.

Despite claims to the contrary, the kinetic similarity of clobazam and diazepam makes it unlikely that clobazam would provide meaningful advantages in clinical practice over what is already available from diazepam.

Conclusion

Evaluation of new anxiolytics in clinical practice—in particular, benzodiazepine anxiolytics—should involve careful metabolic as well as clinical testing. Clinical properties of specific compounds may emerge which are completely unrelated to or are not predicted by pharmacokinetic profiles, as is the case with alprazolam. In other cases, such as with halazepam and clobazam, pharmacokinetic similarities to already available benzodiazepines suggest that these drugs are unlikely to provide meaningful additional benefits. Multidisciplinary evaluation of new anxiolytics is essential to provide the most comprehensive picture of what can be expected from such agents.

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Differentiating Depression and Anxiety: Is It Possible? Is It Useful?[1]

Edna B. Foa, Ph.D.,[2] and Uriel G. Foa, Ph.D.[3]

The terms "depression" and "anxiety" have been used to denote mood states as well as labels for diagnostic categories. As a mood state, depression is characterized by sadness, and anxiety by fear. When these mood states are of high intensity, long duration, and/or frequent, they are considered psychopathological signs or symptoms. When intense sadness appears in combination with other signs or symptoms such as sleep disturbance and loss of appetite, a diagnosis of depression is assigned. When a person with a fear mood state also exhibits autonomic arousal and/or avoidance behaviors, he or she will be diagnosed as "anxious." Thus, "depression" and "anxiety" have been used to denote two distinct syndromes or diagnostic entities.

The relationship between anxiety and depression as diagnostic categories has been the subject of controversy for many years. Some investigators believe that the two syndromes cannot or should not be distinguished, since they constitute manifestations of the same disturbance; others hold the contrary position. A recent comprehensive review of the relevant literature (Roth & Mountjoy 1982) essentially leaves the question open.

The purpose of this paper is twofold: To consider conceptual and methodological problems in the study of the relationships between anxiety an depression, and to present data bearing on th relationship in obsessive compulsives who wer treated with behavior therapy.

Definition and Measurement

The symptoms and signs of the two psycho pathological conditions can be divided into thre classes: 1) signs which are specific to anxiety; 2 those which are specific to depression, and 3 signs which are common to both syndromes. A present, the diagnostic criteria used to classify a patient as depressive also include signs of anxiety Thus, the definition of the two syndromes are no independent of one another. This is also true o the instruments which have been developed t measure depression and anxiety. Having been in fluenced by the traditional diagnostic criteria o the two syndromes, they reflect the overlap bet ween them. The Hamilton Depression Scale, fo example, includes items on insomnia, agitation psychic anxiety, somatic anxiety, and somati symptoms, all contributing to the total score o depression. It is not surprising that this score wil correlate highly with measures of anxiety which also include somatic complaint, agitation, an feelings of doom. The strong influence of th traditional overlay between the two syndromes on the measurement of depression is demonstrated in the argument by Snaith et al. (1971) that the Wakefield inventory constituted a better measure ment of depression than the Beck and Zung in ventories, since the latter failed to include items dealing specifically with anxiety. The remedy of fered for this omission was an assessment tool of depression loaded with items pertaining to anxiety

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[2]Department of Psychiatry, Temple University Medical School, Philadelphia, PA 19129.

[3]Department of Psychology, Temple University, Philadelphia, PA 19122.

Reprint requests should be sent to: Edna B. Foa, Ph.D., Department of Psychiatry, Temple University Medical School at Eastern Pennsylvania Psychiatric Institute, Henry Avenue, Philadelphia, PA 19129.

Snaith et al.'s comments exemplify the absence of conceptual distinction between anxiety and depression which obscures the meaning of the high correlation between the two, often found when assessment by self-reports and by clinical observations was employed. What do these correlations represent? Do they reflect a high joint occurrence between anxiety and depression or are they merely an artifact of the overlap between the definitions and the measurements of the two syndromes?

Another conceptual and methodological problem is embedded in the fact that most instruments designed to measure anxiety or depression yield a single global score. Yet neither of the two is a unitary concept. Rather, each is composed of behavioral, psychophysiological, biochemical, and cognitive-emotional components which are imperfectly intercorrelated. The nature and the degree of the relationship between depression and anxiety may vary greatly, depending on the specific component under investigation. For example, Kelly and Walter (1969) found that the forearm blood flow of nonagitated depressives was less than that of normals, whereas agitated depressed and anxious patients showed increased blood flow. However, when self-reports of anxiety level were examined, the order among the groups changed. Agitated depressives evidenced the lowest level of anxiety, while nonagitated patients rated themselves to be as anxious as those in the anxious group. Thus, in investigating the relationships between anxiety and depression, it seems necessary to study multiple components with the aim of identifying *patterns* of relationships between the two concepts, rather than expecting unidimensional solutions.

The independent definitions of depression and anxiety should each include several component elements. Given the state of the art, however, it seems convenient to start by identifying criteria for classification of the cognitive and the behavioral components which are central to each of the two concepts, and to omit characteristics which are common to both. Measurements for depression and anxiety should be guided by these definitions. Having developed such measurements, we will be better equipped to investigate the relationships between anxiety and depression in various clinical populations, to observe possible changes in these relationships over time, or to examine the effects of anxiety and depression on treatment outcome. This line of investigation will provide an answer to the second question posed: Is the distinction between anxiety and depression useful? Such a distinction is of merit only if there is evidence for different aetiologies, treatments of choice, or treatment outcomes for the two categories.

Differences and Similarities

Notwithstanding the limitation discussed above, the data available point to some differences as well as to certain similarities between anxiety and depression. Not surprisingly, these findings have stoked the fires of proponents of separation (e.g., Roth et al. 1972) as well as of those arguing for unification of the two concepts (e.g., Lewis 1966). Let us consider this evidence briefly.

Psychophysiological Measures

A mixed picture of similarities and differences between depression and anxiety emerges from psychophysiological observations. Lader and his colleagues (Lader 1967, 1976; Lader et al. 1967; Lader & Wing 1964, 1966) demonstrated that patients with anxiety states showed high levels of electrodermal activity and slow habituation of skin conductance responses to repeated auditory stimuli. They also found that complex phobics (i.e., agoraphobics, social phobics, and anxiety states) evidenced more baseline arousal than monophobics with respect to both electrodermal activity and pulse rate; the monophobic group did not differ from normals.

When depressed patients were divided into subgroups of retarded and agitated depressives, differences in electrodermal activity also emerged (Lader & Wing 1969). The agitated depressed patients (who manifest intense anxiety) were more aroused than the retarded groups and, like anxious patients, they habituated more slowly to auditory stimuli than did normals. The retarded group showed almost no electrodermal activity. A similar picture emerged from observations of the cardiovascular responses. As mentioned earlier, Kelly and Walter (1969) found a lower level of forearm blood flow in nonagitated depressed patients than in the agitated depressives. Likewise,

Lader and Wing (1969) reported an increase in pulse rate over normals in agitated but not in retarded depressives. Investigating evoked responses in depressed and anxious patients, Shagass (1955) applied photic stimulation at 10 and 15 Hz to normals, anxiety states, psychoneurotic depressive patients, and psychotic depressives. The ratio of responses at 15 Hz to those detected at 10 Hz was highest in the anxious state patients and lowest for both depressive groups with normals occupying an in between position. The difference among the groups was attributed to differences in the amount of harmonic activity induced by the photic stimulation; again, depressives showed less activity and anxious patients evidenced more activity than normals. It seems, then, that depression suppresses psychophysiological activity whereas anxiety increases it. As stated by Lader (1975), the psychophysiological literature favors a distinction between anxiety and depression "but only if particular care with subgrouping of patients is exercised" (p. 129).

Joint Occurrence

The view that depression and anxiety should be considered a unitary syndrome has been bolstered by the finding that a high proportion of neurotic patients, especially those who are not severely impaired, show both anxiety and depression. So much so that the term anxiety-depression has been proposed by several authors to denote a distinct diagnostic class (e.g., Cooper & Sylph 1973; Snaith 1981). Support for the unitary view is provided by the fact that a relatively high percentage (24 percent) of those who had been diagnosed as being in an anxiety state were rediagnosed several years later as depressives (Kandell 1974). This finding points to the existence of a relationship between anxiety states and depression. However, the fact that only 2 percent of those who were first diagnosed as depressed became anxious at a later time indicates that the two syndromes are distinct. This latter view is further supported by other investigations.

In a series of studies, Roth and his colleagues (Gurney et al. 1972; Roth et al. 1972) examined differences and similarities between patients diagnosed as anxious and those labeled depressed. A first bipolar component of anxiety vs. depre sion emerged when a principal compone analysis was performed on the data. Moreove the presence of an anxiety syndrome decrease the likelihood that a depressive syndrome woul be detected in the same patient and vice versa These results offer strong support for th separatist camp; they should, however, be co sidered with caution since the studies suffer fro several methodological flaws.

Fleiss et al. (1971), in studying 500 admissio to New York and London mental hospitals, foun depression and phobic anxiety to be distinct fa tors. In the total sample 14 subjects were classifie as suffering from anxiety neurosis and 63 we neurotic depressives. When the scores of these p tients on depression and on anxiety were exami ed, the authors found that both groups we equally depressed; but anxiety scores differe tiated the two, being higher in the anxiety grou Further support for the separatist view was pr vided by Prusoff and Klerman (1974) as well as b Downing and Rickels (1974) who were able t separate anxiety from depression on the Hopkin Symptom Checklist. However, a relatively lar overlap betwen the two groups existed (25 to 4 percent) and high correlations between anxie and depression were consistently found. I terestingly enough, Klerman (1980) quoted th above studies in support of the distinction b tween depression and anxiety syndromes where Marks (in press) referred to these same studi when questioning the usefulness of such a separ tion.

A distinction between anxiety and depressio has also emerged from a study on the effects behavioral treatment of obsessive-compulsiv conducted by the first author, (e.g., Foa & Gol stein 1978; Foa et al. 1980; Steketee et al., press). In the course of evaluating the effe tiveness of behavioral treatment, both the patien and an independent assessor rated depression a anxiety *mood states* on 9-point scales which we developed at the Maudsley Hospital in Lond (Watson et al. 1971). Depression was defined loss of interest, crying, pessimistic outloo sadness, and suicidal thoughts. Anxiety w defined as subjective tensions, autonomic arous and motor restlessness. There was almost overlap between the guidelines given to the rate about the type of emotions and behavior th were to consider for determining the scores of t

two variables. Data on levels of depression and anxiety in 71 obsessive-compulsives were thus obtained.

To investigate the joint occurrence of the two variables, patients were divided into three groups with respect to their level of depression. Those whose level of depression was greater than one standard deviation (SD) above the mean were considered "highly" depressed, those whose level was one SD below the mean were labeled "mildly" depressed, and the remainder were classified as "moderately" depressed. The same was done with regard to anxiety. The results were then cross-tabulated. They are given in Table 1.

A strong relationship emerged ($X^2(4) = 16.94$, $p < .01$). However, inspection of the joint occurrence of these variables revealed an interesting pattern. Only 50 percent of the sample fell on the diagonal where the degree of depression and of anxiety were equal. Those who were highly depressed were almost always highly anxious. On the other hand, most highly anxious patients were only moderately depressed. Further, mild depression was associated with *either* moderate or low anxiety. The moderately depressed patients were *either* very anxious or moderately anxious. This asymmetry in the relationships between levels of depression and levels of anxiety suggests that the authors tapped two distinct phenomena and that the relationship found does not merely represent a reliability score for two measures of the same variable.

Table 1

Joint Distribution of Anxiety and Depression Levels in Obsessive-Compulsives Before Treatment

Anxiety	Depression			
	High	Moderate	Mild	Total
High	8	20	2	30
Moderate	1	19	6	26
Mild	0	8	7	15
Total	9	47	15	71

Differences in Responsiveness to Behavioral Treatment

An important criterion favoring a distinction between two conditions is whether they respond differently to treatment. The literature on the effects of psychopharmacological agents on depressed and anxious patients has yielded a mixed picture in this regard and will not be discussed here. Instead, the authors shall consider the differential effects of pretreatment depression and anxiety mood states on effectiveness of behavioral techniques (i.e., exposure and response prevention) with obsessive-compulsive ritualizers. These techniques have been considered the treatment of choice for this disorder (cf. Foa & Steketee 1979). However, several authors suggested that obsessive-compulsives with marked depression do not benefit from treatment by exposure and response prevention as much as those with moderate or mild depression. Indeed, Foa et al. (1982) found that marked depression impeded the immediate effectiveness of behavioral treatment and resulted in a significantly higher rate of relapse.

In a subsequent analysis with a larger sample of 71 patients, the relationship of anxiety as well as of depression to treatment outcome were examined immediately following treatment and at 11 months followup (on the average). The scores for obsessions and compulsions as rated by an independent assessor were combined to yield one score of obsessive-compulsive symptomatology. This score was then converted into a percentage score of change from pretreatment baseline. On the basis of this score, the patients were divided into three groups: those who improved 70 percent or above were labeled "much improved"; those with improvement of 30 to 69 percent were labeled "moderately improved"; patients who failed to show improvement of more than 29 percent were considered "failures". This analysis was performed separately for outcome at posttreatment and at followup.

Prediction from Depression

The relationship between initial depression and treatment outcome was examined with a one-way analysis of variance (ANOVA). Significant differences were detected at posttreatment [$F(2,68) = 6.77$, $p < .002$]. The mean depression scores for those who succeeded, improved, or

failed to benefit from behavioral treatment were 3.15, 4.64, and 5.19, respectively. Posthoc pairwise comparisons using the Bonferoni t-method revealed that the much improved group was significantly less depressed than the moderately improved group ($t = 3.14$, $d.f.$ 68, $p < .01$) than those who failed ($t = 2.88$, $d.f.$ 68, $p < .05$). At followup those who were treated successfully were significantly less depressed than the failures ($t = 2.92$, $d.f.$ 51, $p < .05$), but did not differ from the moderately depressed patients.

The relationship between depression and treatment outcome was further explored by cross-tabulating the data at posttreatment and at followup. These results are given in Tables 2 and 3.

Table 2

Comparison of Initial Depressed Mood with Outcome at Posttreatment

	Depression			
Outcome	High	Moderate	Mild	Total
Much Improved	1	17	12	30
Moderately Improved	7	23	2	32
Failure	2	7	0	9
Total	10	47	14	71

Table 3.

Comparison of Initial Depressed Mood with Treatment Outcome at Followup

	Depression			
Outcome	High	Moderate	Mild	Total
Much Improved	1	17	11	29
Moderately Improved	2	5	2	9
Failure	5	14	0	19
Total	8	36	13	57[a]

[a] At the time this analysis was performed, 14 of the 71 patients had not yet been followed up.

A chi-square performed on these data indicated significant differences at both posttreatment ($X^2(4) = 15.99$, $p = .003$) and at followup ($X^2 = 12.54$, $p = .01$). Inspection of these tables indicates that immediately after 2-3 weeks of daily 2-hour sessions by exposure and response prevention, 12 of the 14 patients who were mildly depressed were much improved, and none failed. The highly depressed groups had one success and two failures; the majority of the patients in this group were moderately improved (*see* Table 2). This pattern became more clear at followup (*see* Table 3). Of the eight patients with marked depression five were failures; none of the mildly depressed patients was a failure and 87 percent were highly improved. Thus, the level of depression at the extremes predicted response to treatment. Patients with marked depression were likely to fail to benefit from behavioral treatment; those with mild or no depression were highly likely to benefit from this treatment.

Table 4

Comparison of Initial Anxious Mood with Outcome at Posttreatment

	Anxiety			
Outcome	High	Moderate	Mild	Total
Much Improved	10	9	12	31
Moderately Improved	16	13	2	31
Failure	5	3	1	9
Total	31	25	15	71

Table 5

Comparison of Initial Anxious Mood with Outcome at Followup

	Anxiety			
Outcome	High	Moderate	Mild	Total
Much Improved	11	7	11	29
Moderately Improved	3	3	3	9
Failure	11	8	0	19
Total	25	18	14	57[a]

[a] At the time this analysis was performed, 14 of the 71 patients had not yet been followed up.

Prediction from Anxiety

A different picture emerged for the investigation of the relationship between anxiety and treatment outcome, although anxiety was also found related to responsiveness to behavioral treatment. (At posttreatment $F[2,68] = 4.99$, $p < .01$; at followup $F[2,51] = 3.24$, $p < 05$.) When degree of anxiety was cross-tabulated with degree of success in behavioral treatment, a significant relationship was again detected (At posttreatment

$X^2(4) = 10.53$, $p < .03$; at followup $X^2(4) = 9.56$, $p = < .05$.)

However, the pattern for anxiety as a predictor of treatment outcome differed from that for depression. At posttreatment (*see* Table 4) one third of the highly anxious patients were much improved, although their chances were not as good as those who were initially mildly anxious. Among the latter, most were much improved and only one failed. A similar pattern emerged at followup (*see* Table 5).

In summary, mild depression predicted success and high depression predicted failure of behavioral treatment with obsessive-compulsives. By contrast, even a high level of anxiety was associated with good response to treatment. This pattern became more pronounced at followup (*see* Tables 3 and 5). Marked depression predicted failure, whereas high anxiety was equally associated with success and with failure.

Conclusion

The mood states of anxiety and depression have yielded a somewhat different prognosis in the study reported here, despite the crude measurements which have been employed. The existence of such a difference indicates that a distinction between depression and anxiety might be useful for predicting the outcome of behavioral treatment. Paradoxically, such a distinction is also a *sine qua non* for the investigation of the empirical joint occurrence of anxiety and depression, an issue that has gained much attention in the psychiatric literature. Only definitions which are independent of one another will lead to the construction of instruments of depression and anxiety which will not overlap each other. Only such instruments may yield valid data for the understanding of the relationship between two concepts.

Each instrument should include items from several components (at least from the cognitive and behavioral domains) and each should exclude items which are common to the two syndromes. In essence, then, the investigation of the relationship between depression and anxiety will involve comparisons of several clusters of observations rather than of two single indices composed of a variety of symptoms which has been forcibly combined. The results so obtained will hopefully contribute to a more lucid conceptualization of the two syndromes. As the relationship between concepts and data is a reciprocal one, more precise concepts lead to better measurements which, in turn, yield information that further clarifies theoretical issues.

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Differentiating Anxiety and Depression in Anxiety Disorders: Use of Rating Scales

Ronald S. Lipman, Ph.D.[1]

Both anxiety and depression have been conceptualized as normal affects or moods, as symptoms (when their intensity or duration persists beyond "normal" limits), as syndromes (when a cluster of co-occurring symptoms are identified), and as diagnostic entities (when notions of differential etiology, prognosis, and/or treatment response as well as boundaries between mental disorders are employed) (Diagnostic and Statistical Manual-III 1980; Lehmann 1966).

This paper will focus on differentiating anxiety and depression at the level of syndromes and diagnoses. It should be made clear that while some writers consider anxiety and depression as phenomenally indistinguishable (e.g., Lewis 1966), the overwhelming consensus in the field is that these two affective disorders are separable and, indeed, that neither anxiety nor depressive disorders are themselves single mental disorders. This area has recently been reviewed by McNair and Fisher (1978) and, indeed, the reader is probably familiar with both statistical typologies such as Overall et al. (1966) (based on Brief Psychiatric Rating Scale scores on Anxious, Hostile, Agitated, and Retarded Depression), and clinical typologies such as Klein's (1974) concept of reactive, endogenomorphic, and neurotic depression. Since the Diagnostic and Statistical Manual-III (DSM-III) (1980) differentiates among and between anxiety disorders and affective disorders, which subsume depresssion, it is probably worthwhile to examine the DSM-III classification of primary anxiety disorders. In this regard, DSM-III, as a result of the research of Klein (1978), differentiates between Panic Disorder and Generalized Anxiety Disorder, both characterized by free or manifest anxiety, and Phobic and Obsessive-Compulsive Disorders, where the patient goes to extremes to avoid experiencing the anxiety of either the dreaded object or situation or of the resisted obsession or compulsion. A good description of Phobic and Anxiety States, based on DSM-III, has been developed by Davis et al. (1981) and is presented in Table 1.

Table 1

Diagnostic Description of Phobic Disorders and Anxiety State

Sudden spontaneous unexplained panic attack characterized by feeling of terror, autonomic symptoms of anxiety, and flight response
Symptoms during an attack may include:
Anxiety, terror, helplessness, impending doom
Smothering or choking feeling, difficulty getting breath
Dizziness or faintness
Trembling
Tingling, hot or cold spells
Chest pain or discomfort
Nausea
Palpitation and rapid heart beat
Sudden empty feeling in pit of stomach
Fear of places where attack occurs
Public places (restaurants, stores, buses)
Fear that one cannot reach secure place such as home

[1]The Johns Hopkins University School of Medicine, The Henry Phipps Psychiatric Clinic, Baltimore, MD 21205.

Table 2

RDC Inclusion Criteria for Major Depressive Disorders: The Presence of a-d Are Required

YES	NO	(a)	Dysphoric mood or pervasive loss of interest or pleasure. The period(s) of dysphor mood is/are characterized by such symptoms as "depressed, sad, blue, hopeless, down in the dumps, don't care anymore or irritable."
YES	NO	(b)	At least *five* of the following symptoms are necessary to have occurred as part of the episode for "definite" depression and *four* for "probably" depression.
YES	NO		(1) Poor appetite or weight loss or increased appetite or weight gain (change of 1 pound a week of 10 pounds a year with no dieting).
YES	NO		(2) Sleep difficulty or sleeping too much.
YES	NO		(3) Loss of energy, fatigability, or tiredness.
YES	NO		(4) Psychomotor agitation or retardation (but not mere subjective feeling of restlessness or being slowed down
YES	NO		(5) Loss of interest or pleasure in usual activities, including social contact or sex (not included or limited to a period when delusional or hallucinating). (The loss may or may not be pervasive).
YES	NO		(6) Feelings of self-reproach or inappropriate guilt (either may be delusional).
YES	NO		(7) Complaints or evidence of diminished ability to think or concentrate, such as slowed thinking, or indecisiveness (do not include if associated with marked formal thought disorder).
YES	NO		(8) Recurrent thoughts of death or suicide, or any suicidal behavior.
YES	NO	(c)	Duration of dysphoric features at least 1 week beginning with the first noticeable change in the subject's usual condition ("definite" means lasted more than 2 weeks, "probably" if 1 to 2 weeks).
YES	NO	(d)	Sought or was referred for help from someone during the dysphoric period, took medication, or had impairment in functioning with the family, at home, at school, or socially.

The Phobic Disorders are subdivided into agoraphobia (with or without panic attacks), Simple Phobia, and Social Phobia.

DSM-III also recognizes and defines a number of depressive disorders based on such considerations as severity, and whether or not there has been a history of manic or hypomanic features (see DSM-III, pp. 220-224). Since a number of large-scale collaborative studies are employing the Research Diagnostic Criteria (RDC) for Major Depressive Disorder (Feighner et al. 1972), these inclusion criteria are summarized in Table 2.

In practice, many research studies focused on the evaluation of pharmacotherapy and/or psychotherapy for the treatment of nonpsychotic, nonbipolar, depressed outpatients, as well as studies on nonpsychotic outpatients. These studies have employed rating scales and checklists to help define their anxious and depressed cohorts (e.g., Lipman et al. 1981). In this regard, two relatively simple physician rating scales have been developed by Raskin and by Covi (Lipman et al. 1981). Each scale employs three subscales which tap the dimensions of verbal report, behavior, and somatic symptoms. Typically, a minimal severity sum of 7, 8, or 9 has been employed on these scales (range from 0 to 15) to select patients with sufficient severity of anxiety and/or depresssion to qualify the patient for inclusion in treatment outcome studies with antidepressant and/or antianxiety medications. The Covi Anxiety Scale is presented in Table 3 and the Raskin Depresssion Scale is shown in Table 4.

Table 3

Anxiety Scale (Covi)

not at all	somewhat	moderately	considerably	very much	
1	2	3	4	5	**Verbal Report:** Feels nervous, shaky, jittery, jumpy, suddenly scared for no reason; fearful, apprehensive, tense or keyed up; has to avoid certain things, places, activities because of getting frightened; finds it hard to keep mind on task.
1	2	3	4	5	**Behavior:** Appears frightened, shaking, restless, apprehensive, jumpy, jittery.
1	2	3	4	5	**Somatic Symptoms of Anxiety:** Unjustified sweating, trembling; heart pounding or racing; trouble getting breath; hot or cold spells; restless sleep; going unjustifiably more frequently to bathroom; discomfort at pit of stomach; lump in throat.

Table 4

Depression Scale (Raskin)

not at all	somewhat	moderately	considerably	very much	
1	2	3	4	5	**Verbal Report:** Feels blue; talks of feeling helpless, or worthless; complains of loss of interest; may wish to be dead; reports of crying spells.
1	2	3	4	5	**Behavior:** Looks sad, cries easily, speaks in a sad voice; appears slowed down; lacking energy.
1	2	3	4	5	**Secondary Symptoms of Depression:** Insomnia or hypersomnia; G.I. complaints; dry mouth; history of recent suicide attempt; lack of appetite; difficulty in concentrating or remembering.

In addition to these very simple scales, the study utilized other physician (therapist) rating scales, namely, the American College of Neuropsychopharmacology (ACNP) Checklist for Anxiety and Depression (Wittenborn 1977); and the Hamilton Anxiety and the Hamilton Depression Scales (ECDEU Assessment Manual 1976). Since the ACNP Anxiety and Depression checklists are not generally available, and since these scales were specifically developed as guidelines for the Food and Drug Administration (FDA) in evaluating the adequacy of subject selection for trials of antianxiety and antidepressant medications, respectively, they are presented here in Tables 5 and 6.

Table 5

ACNP Depression Checklist

YES	NO	Main Symptoms
____	____	Dysphoric Mood (depressed, sad, despondent, hopeless, down in the dumps, discouraged).
		Associated Symptoms
____	____	Poor appetite and weight loss (2 lbs per week or 10 lbs per year, if not dieting).
____	____	Sleep difficulty (insomnia or hypersomnia)
____	____	Loss of energy (fatigability, tiredness)
____	____	Agitation or retardation
____	____	Recent loss of interest in usual activities and decreased libido
____	____	Self-reproach or guilt feelings
____	____	Complaints of (or actually diminished) thinking and concentration (slow thinking, mixed-up thoughts)
____	____	Recurrent thoughts of death or suicide, wish to be dead
____	____	Anhedonia (inability to experience pleasure)
____	____	Bodily complaints.

It should be noted that the ACNP Anxiety guidelines require "moderate" levels, or higher, on the first two manifestations (feeling nervous, jittery, jumpy; feeling fearful, apprehensive, anxious, panicky) and at least three other symptoms and signs of anxiety. The syndrome definition of depression requires depressed mood (characterized by "sad, low, blue, despondent, hopeless, gloomy") plus four or five of the associated symptoms. It is interesting to note that anxiety and tension (Item 14) and agitation (Item 6) which are included as symptoms of the depressive syndrome are also contained as part of the symptomatology of the anxiety syndrome. Similar overlaps of symptomatology, i.e., sleep disturbance, are also present on the Hamilton Anxiety and Hamilton Depression Scales. The members of the ACNP task force that drafted these guidelines were aware of the issues around the separation and overlap among patients with anxiety and/or depression.

In this regard, they indicate "the coexistence of anxiety and depression...also presents a special problem. Although the two states frequently occur together in varying degrees, most patients can be classified as primarily anxious or primarily depressed." (p. 220)

Table 6

ACNP Anxiety Checklist

YES	NO	Main Symptoms
____	____	Feeling nervous, jittery, jumpy
____	____	Feeling fearful, apprehensive, anxious, panicky
		Associated Symptoms
____	____	Fears of fainting, screaming, losing control, crowds, places, disaster, death
____	____	Avoiding certain places, things or activities because of fear
____	____	Feeling tense or keyed up
		Muscular or Motor Phenomena
____	____	Tense Muscles, aches
____	____	Trembling, shaking
____	____	Restlessness, fidgeting
		Autonomic Phenomena
____	____	Heart beating fast or pounding; chest pain
____	____	Trouble catching breath, air hunger, smothering, lump in throat, choking
____	____	Sweating, especially armpits, palms, soles of feet
____	____	Cold clammy hands
____	____	Dry mouth
____	____	Dizziness, faintness, lightheadedness, weakness
____	____	Tingling feelings in hands or feet
____	____	Stomach "gas," nausea, upset stomach

Table 7

HSCL Anxiety Cluster

Items	R11
Nervousness or shakiness inside	
Heart pounding or racing	
Sweating	
Suddenly scared for no reason	
Trouble getting your breath	
Trembling	
Hot or cold spells	
Feeling tense or keyed up	
Faintness or dizziness	
Feeling fearful	
A lump in your throat	0.80

Table 8

HSCL Depression Cluster

Items	R11
Feeling low in energy or slowed down	
Thoughts of ending your life	
Poor appetite	
Feeling blue	
Feeling no interest in things	
Feeling hopeless about the future	
Blaming yourself for things	
Loss of sexual interest or pleasure	
Crying easily	
Feeling lonely	
Constipation	0.81

In addition to the use of therapist rating scale to help select anxious or depressed patients, many research teams also make use of patient self-ratings. Among the most frequently used of the patient self-rating scales is the Hopkins Symptom Checklist (Lipman et al. 1979). Normative data are available for the 58-item version of this Scale (Derogatis et al. 1974) and many investigators have required that patients rate themselves at a level of distress on the Anxiety and/or Depression Clusters at least two standard deviations higher than the means of the normative sample, i.e., a score of 1.65 on the Anxiety Cluster and a score of 1.70 on the Depression Cluster. The items that define these clusters are presented in Tables 7 and 8.

The clusters themselves reflect the consensus among experienced clinicians that the items subsumed in each cluster reflect either anxiety or depression (Lipman et al. 1968). In this regard, there was at least 75 percent agreement among each of 20 experienced clinicians that the items given in Tables 7 and 8 reflected either anxiety or depression. The Hopkins Symptom Checklist (HSCL) was employed by Prusoff and Klerman (1974) in a study of anxious and depressed outpatients who participated in trials of antianxiety and antidepressant medications, respectively. The depressed sample consisted of patients who were treated in either New Haven or Baltimore; the anxious patients all had participated in controlled psychotropic drug trials at the Johns Hopkins University and were selected from a much larger data file to match the depressed sample on age, sex, and social class. A discriminant function analysis was employed to determine whether or

ot the five factors of the HSCL would reliably ifferentiate the anxious and depressed samples. Vhile the 66 percent discrimination of diagnostic roups was reliably better than would by expected y chance, these data suggest considerable verlap among diagnostic groups. The main iscrimination in this study was derived from the omatization factor of the HSCL which was igher in the anxious sample despite the generally igher level of distress in the depressed group. he use of the individual items of the HSCL did ot add much to the separation of diagnostic roups. In an earlier less systematic study by ellner et al. (1972), somatic symptoms were also ound to occur more with anxiety than with epression.

In a very large sample collaborative study supported by the Pharmacologic and Somatic Treatments Research Branch of the National Institute of Mental Health, Johns Hopkins University (L. Covi, Principal Investigator), Boston University (D. McNair, Principal Investigator), and the University of Pennsylvania (K. Rickels, Principal Investigator), the issue of the distinctiveness between anxiety states and depressed disorders was addressed within the context of a placebo-controlled drug trial which employed tranquilizers and tricyclic antidepressants. The preliminary results of this study were reported at the December 1980 meeting of the ACNP, and four papers were subsequently published in the July 1981 issue of the *Psychopharmacology Bulletin* (Covi et al. 1981; Downing et al. 1981; Kahn et al. 1981; Lipman et al. 1981).

In order for outpatients to be selected for this study, they must have self-rated themselves as significantly anxious and/or depressed on the corresponding HSCL clusters of Anxiety (1.65 or higher) or Depression (1.70 or higher) and must also have been rated at least "moderately" anxious and/or depressed by the intake psychiatrist on the Raskin and/or Covi screens (8 or higher). Additionally, the patient must have been anxious and/or depressed for at least 2-3 weeks prior to intake and must not have ever been schizophrenic, alcoholic- or drug-addicted, mentally retarded, organically impaired, sociopathic, or bipolar.

In addition to these main inclusion and exclusion criteria, patients were also classified by DSM-II criteria and according to categories of anxiety and/or depression as proposed by such investigators as Klein and Davis (1969) and Overall et al. (1966). Since the primary purpose of the study was to assess the clinical response of anxious and depressed outpatients to commonly employed anxiolytics and antidepressants, the reliability with which these groups can be identified and the distinctiveness of the groups in terms of diagnosis and presenting symptomatology is critical. In order to address these issues, each patient was classified as primarily anxious or primarily depressed on three separate occasions: 1) by an intake psychiatrist; 2) 1 week later by the psychiatrist who treated the patient; and 3) by this same treating psychiatrist after the patient had completed a 2-week placebo washout period. The agreement in diagnostic assignments was reflected by Kappas of .62 between the intake and treating psychiatrists and .73 between the same psychiatrists before and after the 2-week placebo period. Eighty-seven percent of the patients classified as depressed at intake and 75 percent of those classified as anxious at intake were again so classified by an independent psychiatrist 1 week later. These respective proportions were 90 and 83 percent in the ratings of the same psychiatrists which were made 2 weeks apart. Clearly, then, the assignment of anxious and depressed patients to diagnostic groups has been made with reasonable reliability.

In addition to the scales already mentioned, the study also employed the Hamilton Anxiety and Hamilton Depression Scales and the ACNP Checklist for Anxiety and for Depression. A typical psychiatric and family history was also collected on each patient, and DSM-II diagnoses were made. Not surprisingly, 93 percent of the patients judged to be primarily anxious received the diagnosis of Anxiety Neurosis, whereas about 88 percent of those patients classified as primarily depressed were given the diagnosis of Depressive Neurosis. Other diagnostic details are given in Downing et al. (1981).

Although there was considerable overlap in levels of anxiety and depression between the 424 patients classified as primarily depressed and the 240 patients classified as primarily anxious, each scale reliably differentiated between the diagnostic groups in the expected direction. On the Covi Anxiety Scale the mean for the anxious group (10.4) was significantly higher ($p < .001$) than the mean (8.31) for the depressed group. On the Raskin Depression Scale the mean for the depressed (10.4) sample was reliably higher

($p < .001$) than the mean for the anxious (7.65) sample. Statistically significant differences of roughly comparable magnitude were also found when the mean scores of the anxious and depressed groups were contrasted on the ACNP checklists of Anxiety and Depression. Similar results were also observed for the Hamilton Anxiety and the Hamilton Depression Scales. The results for the ACNP Anxiety and Depression Checklist are shown in Figure 1.

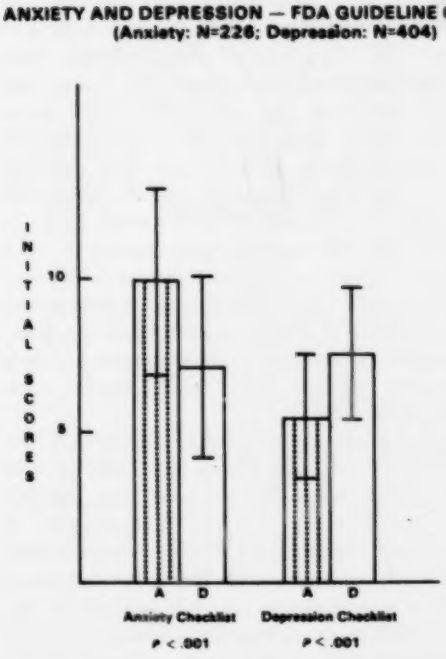

FIGURE 1

The results obtained on the HSCL agree with the prior findings of Downing and Rickels (1974), "...anxiety and depression dominated the symptom profiles of all patients, but in anxiety study patients, anxiety was the more severe...while in depression study patients, depression was the more severe." In the present study, mean cluster scores for the anxious group were significantly higher for Anxiety ($p < .025$) and Somatization ($p < .025$) whereas in the depressed group, mean scores were higher on the Depression ($p < .001$), Obsessive-Compulsive ($p < .001$), and Anger-Hostility ($p < .025$) clusters. In the depressed group, the ranking of symptom distress from hi to low was Depression, Obsessive-Compulsiv Anxiety, Somatization, and Anger-Hostility. Th corresponding ranking in the anxious group wa Anxiety, Depression, Obsessive-Compulsiv Somatization, and Anger-Hostility. A somewh more fine-grained breakdown of symptom profil for the nine apriori factor scores postulated to b contained in the 90-item version of the HSCL presented in Figure 2.

As expected, the anxious group self-ra themselves higher than the depressed group o items contained in the Phobic-Anxiety clust ($p < .001$). When the relative rankings of the nin clusters of the HSCL are compared in the anxio and depressed groups, it is of interest that th rank-order correlation (RHO) of .87 ($p < .01$) i quite high. This indicates that, despite th statistically significant differences in level o distress on these dimensions of symptomatolog the pattern or profile of distress is quite similar i primarily anxious and primarily depressed pa tients. Indeed, were it not for the differences be tween groups in the relative rank ordering of anx iety (1.5 in the anxious group vs. 6 in the depres ed group) and depression (4 in the anxious vs. 1 i the depressed), the correlation in ranks would b almost perfect.

To further pursue the question of qualitativ differences in symptomatology between th primarily anxious and primarily depresse groups, the RHO among the 17 items comprisin the depression cluster and the RHO among the 1 items comprising the anxiety cluster wa calculated. For the depressed vs. anxious grou on the Depression cluster the rho was .95 ($p < .0$ while the RHO was .88 ($p < .05$) between group on the Anxiety cluster. In fact, the RHO of .7 was significant across groups on the 6-item Phobic-Anxiety cluster. Clearly, then, there i both a remarkable similarity of symptom profile across the various domains of outpatient distres as well as within the more specific areas o depressive and anxious symptomatology. I should also be made clear to the reader that th symptom levels of nonpatient groups ar remarkably low and very significantly differen statistically than the observed levels in our anx ious and depressed groups (Derogatis et al. 1974).

In a further step to explore differences in symp tomatology between anxious and depresse samples, the specific symptoms which were rate

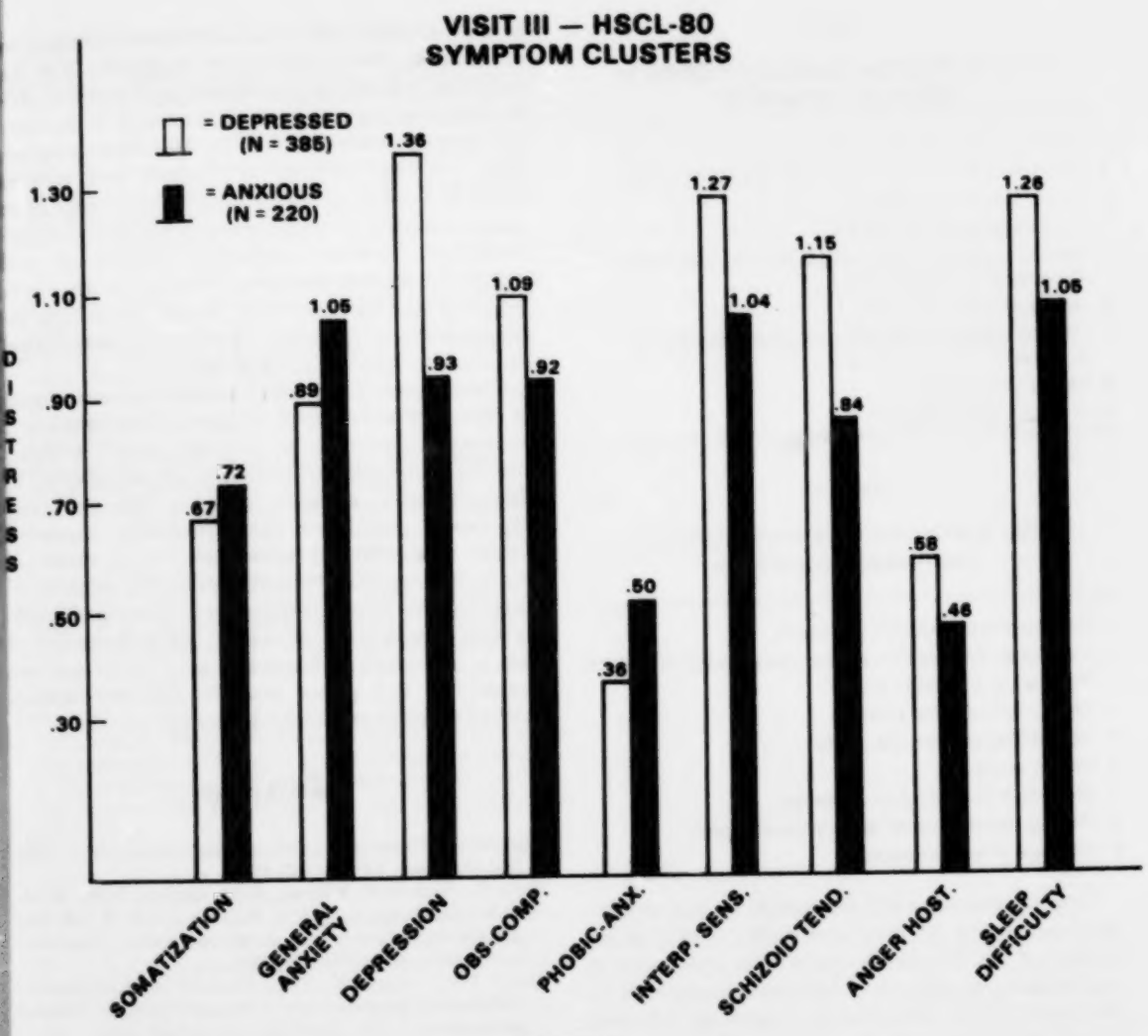

FIGURE 2

higher by anxious than depressed patients are presented in Table 9. The items comprising this table are clinically very meaningful and, in DSM-III terminology, they are associated with the diagnosis of Agoraphobia with Panic Attacks.

A similar analysis of items rated higher by depressed than anxious patients was cut off after nine items, since the depressed sample was relatively more distressed on all the items of the HSCL-80 with the exception of those items listed in Table 9. The nine items rated highest by the depressed group are presented in Table 10. First, it is clear that all the items in Table 10 are reflective of depression and, second, that the depression has an endogenous quality. Again, these are a very meaningful cluster of symptoms.

Table 9

HSCL Symptoms Relatively Highest in Anxious Outpatients

1. Feeling afraid you will faint in public
2. Numbness or tingling in parts of your body
3. Heart pounding or racing
4. Trouble getting your breath
5. Having to avoid certain things, places, or activities because they frighten you
6. Spells of terror or panic
7. Feeling uneasy in crowds such as shopping or at a movie
8. Hot or cold spells
9. A lump in your throat

Table 10

HSCL Symptoms Relatively Highest in Depressed Outpatients

1. Feeling hopeless about the future
2. Feeling all the pleasure and joy has gone out of your life
3. Feeling no interest in things
4. Thoughts of ending your life
5. Not getting any fun out of life
6. Crying easily
7. Sleep that is restless or disturbed
8. Feeling you may never enjoy yourself again
9. Feelings of worthlessness

One cannot help but be struck by the conclusion reached by McNair and Fisher (1978) in the review of the Newcastle study that attempted to discriminate anxious and depressed inpatients on the basis of their initial symptomatology. McNair and Fisher indicated: "several single symptoms correctly classified the sample...a little reflection on these symptoms suggests that panic anxiety versus endogenous depression or agoraphobia versus endogenous depression might more precisely name the factor."

As was pointed out early in this paper, neither anxiety disorders nor depressive disorders are unitary illnesses, and it would seem easier to differentiate certain types of anxiety disorders from certain types of depressive disorders. Again, these distinctions seem to be quantitative, rather than qualitative.

It should be noted that other domains than symptomatology as assessed by rating scales can be used to differentiate anxiety and depression. In this regard, Beck (1971) has suggested that the cognitive schemata characterizing depression differ from the cognitive schemata found in anxiety. He stresses themes of loss as underlying depression, whereas themes of danger are said to underlie anxiety. Biological differences such as in blood flow and in cortisol secretion probably differentiate between primarily depressed and primarily anxious patients. Psychiatric history in terms of age of onset and family psychiatric illnesses are also relevant. Finally, it is also critical to consider treatment response.

The results of the collaborative study discussed in the present paper suggest that treatment response differences to tricyclic antidepressants and to minor tranquilizers are not as different in the primarily anxious and in the primarily depressed population as previously supposed (Kahn et al. 1981). On the other hand, there are clinically important differences in the relative efficacy of the minor tranquilizer chlordiazepoxide in both populations. However, a full discussion of this more subtle difference would go beyond the bounds of this paper and the still preliminary nature of some of the data analytic results.

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Are There Anticompulsive or Antiphobic Drugs? Review of the Evidence

Isaac Marks, M.D.[1]

This paper summarizes a more detailed review of controlled studies of antidepressants for phobic and obsesssive-compulsive disorders (Marks et al. in press). Despite their impressive differences in phenomenology, obsessive-compulsive and phobic disorders are dealt with together because they share common features of avoidance and accompanying discomfort as well as frequently coexisting dysphoria* (anxious-depressed mood), and both respond similarly to antidepressants and to behavioral treatments.

A literature search found 12 controlled studies of antidepressants for predominantly phobic and 4 for predominantly obsessive-compulsive problems which satisfied the criterion of a minimum of 8 patients who completed drug treatment (Ananth 1980; Gittelman-Klein & Klein 1971; Insel et al. 1982; Lipsedge et al. 1973; Marks et al. 1980, in press; Mavissakalian & Michelson 1982; McNair & Kahn 1981; Mountjoy et al. 1977; Pecknold et al. 1980; Sheehan et al. 1980; Solyom et al. 1981; Thorén et al. 1980; Tyrer et al. 1973; Zitrin et al. 1978, 1982). All reported drug dosages in the moderate-high range usually considered adequate for depressive illnesses. All concerned mainly female, adult populations aged 20-60 with problems which have usually been there from 1-10 years or more. Most concerned outpatients, though three involved inpatients who were obsessive-compulsive (Insel et al., 198 Marks et al. 1980; Thorén et al. 1980). Th phobics were largely agora- and social with pan attacks and anxiety-depression (dysphoria). Th latter concerns symptoms, not diagnosis, as mo studies excluded patients who had either seve depression as a symptom or depresssive illness a a diagnosis. One study concerned school phobi (Gittelman-Klein & Klein 1971) and another in cluded a group of simple phobics (Zitrin et a 1978).

Anxiety-Depression and Outcome

One predictor of drug effect seems to be th *starting level of dysphoria*, drug effects generally be ing absent where this is low. Lack of commo measures across studies complicates the task, bu five paired comparisons were possible of studie with common measures (Insel et al. 1982; Mark et al. 1981, in press; Mavissakalian & Michelso 1982; Sheehan et al. 1980; Solyom et al. 1981 Zitrin et al. 1980). In four of the five com parisons, the studies reporting drug effects ha significantly higher starting levels of dysphori than those finding no drug effects. The exceptio is Zitrin et al.(1980), whose patients had as low a rating as those of Marks et al. (1982) on the singl depressive item on which they could be compared (Klein, personal communication).

Table 1 shows a detailed comparison betwee Sheehan et al. (1980) and Marks et al (1982)—the latter's London sample tended to be *more* agoraphobic as well as *less* dysphoric than the former's Boston sample. This indicates that Lon don and Boston patients did not differentially re spond high or low to questions as a whole (no dif

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[1]Institute of Psychiatry, London SE5 8AF, England. (This study was done while Dr. Marks was at the Center for Advanced Study in the Behavioral Sciences, Stanford, California.)

*"Dysphoria" here denotes symptoms of anxiety-depression, not the diagnosis of the syndromes of generalized anxiety state, dysthymia, or depressive illness. Anxiety and depression overlap so much both as symptoms and as syndromes that they are often indistinguishable (reviewed by Marks 1981b).

erence in response set), but rather to certain ypes of symptoms (they differed in the kinds of ymptoms they emphasized. These comparisons ighlight the difficulty in obtaining closely comarable populations across centers merely by tilizing diagnostic categories alone, and illustrate he additional need to report initial phenomenological features on standard measures.

Table 1

Comparison of Initial Scores of Agoraphobics of Marks et al.[a]1982 (M) and Sheehan et al. 1980 (S)

		a None or Mild (Percent)	b Moderate (Percent)	c Extreme (Percent)
Depression				
(S) Feeling blue	$N = 57$	28	40	32[b]
(M) Feeling miserable or depressed	$N = 45$	55	32	13[b]
Agoraphobia				
(S) Phobia: Going out of house alone	$N = 57$	25	19	56[c]
(M) Phobia: Going out alone far from home	$N = 45$	16	11	73[c]

[a] none or mild = score 0, 1, or 2; moderate = score 3, 4, 5; extreme = score 6, 7, or 8.
[b] χ^2 $p < .01$ (a vs. b vs. c)
[c] χ^2 $p < .07$ (a + b vs. c)

Table 2

Outcome Versus Initial Depression Score (Controlled Studies of Phobics and Obsessive-Compulsives)

Drug Effect	Initial Mean Depression Score: Moderate	Moderate-Mild	Mild-Absent
Present	Sheehan et al. (1980)	Tyrer et al. (1973)	?Zitrin et al. (1980)
	McNair & Kahn (1981)	Zitrin et al. (1980)	
	Pecknold et al. (1980)	Mavissakalian & Michelson (1982)	
	Ananth et al. (1980)	Gittelman-Klein & Klein (1971)	
	Marks et al. (1980)	Insel et al. (1982)	
	Thoren et al. (1980)		
Absent			Marks et al. (1982)
			Solyom et al. (1981)
			Marks et al. (1980)
			Thoren et al.[a] (1980)

[a] See analysis of subsamples by Marks (1981, p. 178) and Table 1 of Thoren et al. (1980).
Initial depression scores not reported:
Drug effect present: Lipsedge et al. (1973)
Zitrin et al. (1978)
Drug effect absent: Mountjoy & Roth (1974)

A coarser way of judging the effect of dysphoria is by grouping the studies according to initial levels of dysphoria, regardless of the particular measure used (Table 2). Levels are based on scores reported elsewhere (Marks, in press-b). The lower right sector of Table 2 shows that in those four studies where a drug effect was absent the starting level of dysphoria was especially low. The placing of the study of Zitrin et al. (1980) is unclear, because on the Brief Psychiatric Rating Scale (BPRS) the sample would be rated as mild-moderately dysphoric, yet on another item (Table 1, and Klein, personal communication) it would be mild-absent.

Within three of the studies on obsessive-compulsives, direct comparison was possible between patients with the highest and the lowest levels of initial dysphoria. Two of these comparisons showed that the effect of clomipramine was exclusively attributable to those patients with the highest levels of dysphoria at the start, and was absent in those with initially low levels. Table 3 displays the data for clomipramine patients taken from Table 1 of Thorén et al. (1980).** Three of the eight clomipramine patients had secondary depression and these three responded in the open part of the study, while only one of the five without secondary depression was a drug responder (these were also the five patients with the highest plasma levels of clomipramine—Åsberg, personal communication). During the 5-week controlled phase of the study, pa-

**The Childrens' Psychiatric Rating Scale depression improvement scores were kindly supplied by Dr. Marie Åsberg.

Table 3

Effect of Depression on Outcome of Obsessive-Compulsive Disorders (From Table 1, Thorén et al. 1980)

Patient's Sex/Age	Secondary Depression?	Responder in Open Study After 5 Weeks?	Improvement At 5 Weeks: Obsessional Symptoms	OCD Scale	Depression
M44	yes	yes	2.5	9.0	8.0
F50	"	"	2.0	7.5	9.0
F28	"	"	3.0	7.5	9.5
			$\bar{x}$ 2.5	$\bar{x}$ 8.0	$\bar{x}$ 8.8
F36	no	no	1.5	.0	5.5
F32	"	"	1.0	5.0	2.0
F35	"	"	1.5	2.5	2.0
F20	"	"	.0	1.0	2.5
F55	"	yes	.0	4.0	4.5
			$\bar{x}$ 0.8	$\bar{x}$ 2.5	$\bar{x}$ 2.9

tients with initial depression subsequently improved significantly less than those without depression (analysis of variance).

The Figure shows a similar analysis for th ritualizers of Marks et al. (1980); here the tw samples represented the highest and lowest quar tiles for depression on the Hamilton an Wakefield scales. Again, the clomipramine effe occurred exclusively in those with the highest sta ting levels of depression. Further analysis of the patients (Mawson et al. 1982) found that a singl 0-8 scale for initial free-floating *anxiety* was almo as good a predictor of clomipramine effect as wa depression, which is not surprising given their in tercorrelation of .70, but suggests that we shoul speak of dysphoria rather than depression.

A third comparison had discordant finding Insel et al. (1982, personal communication) com pared outcomes of his obsessive-compulsives wit the highest and lowest initial depression scale and found that both subsamples retained th superiority of clomipramine over clorgyline.

Among phobics, McNair and Kahn (198 found that imipramine had no significant drug e fect on agoraphobia overall; a significan agoraphobia × depression interaction indicate

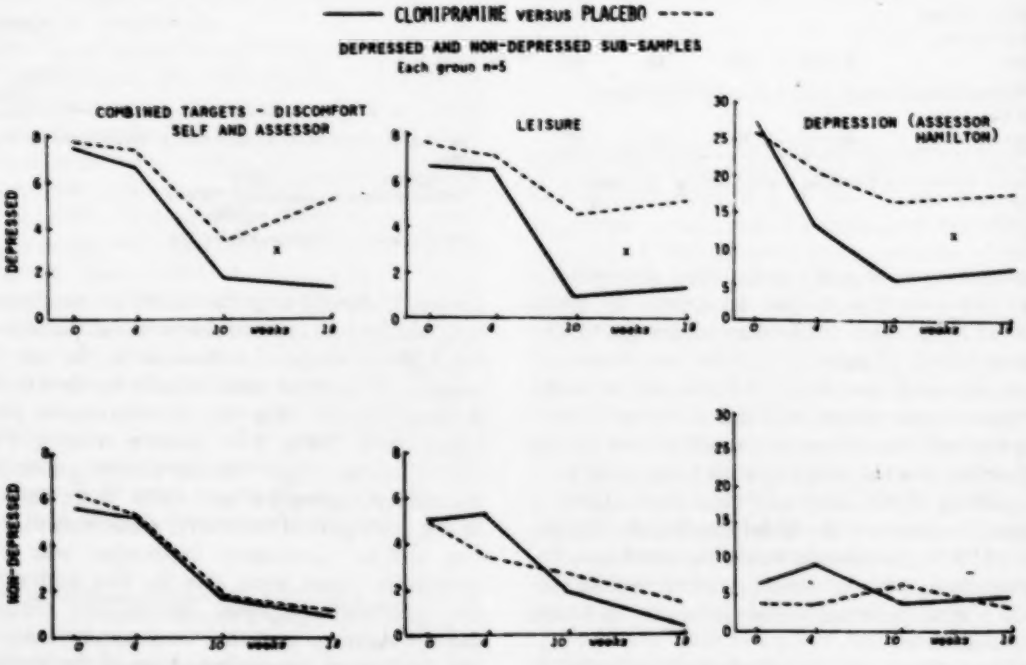

FIGURE. Outcome of ritualisers with clomipramine: Initially high vs. initially low depression (from Marks et al. 1980).

that imipramine reduced agoraphobia only when it was accompanied by depression. Imipramine did produce a significant reduction in depression and also in panics independently of depression.

Zitrin et al. (1980) found a negative correlation between starting level of depression and several measures of outcome, but did not compare outcomes of those with the highest and lowest starting levels, which might have detected effects obscured by their many patients in the middle starting level. The potential importance of this point is testified by the obvious relationship between initial depression and outcome in the ritualizers of Marks et al. (1980) when the top and bottom quartiles were compared, but the virtual disappearance of this relationship when it was sought for in the entire sample (Raskin, personal communication). Sheehan et al. (1980) found no relationship between five vegetative signs of endogenous depressive illness and outcome. Working with their data, this author could also find no relationship between outcomes contrasted in patients with the highest and the lowest levels of initial depression. However, even those with the lowest levels had fairly high starting levels (only two had Zung scores below 55). Table 2 suggests that there may be a threshold of moderate dysphoria below which a drug effect is unlikely, and the Boston sample had too few cases without dysphoria to test this hypothesis.

Of the twelve studies in adult phobics (Lipsedge et al. 1973; Marks et al., 1980, in press; Mavissakalian & Michelson 1982; McNair & Kahn 1981; Mountjoy et al. 1977; Pecknold et al. 1980; Sheehan et al. 1980; Solyom et al. 1981; Tyrer et al. 1973; Zitrin et al. 1978, 1980), five found no drug effect on phobias (Lipsedge et al. 1973; Marks et al., in press; McNair & Kahn 1981; Mountjoy et al. 1977; Solyom et al. 1981). Of these five, two had patients with low initial levels of dysphoria (Marks et al. in press; Solyom et al. 1981), one found an antidepressant and antipanic but no antiphobia effect (McNair & Kahn 1981), and two did not report initial depression levels (Lipsedge et al. 1973; Mountjoy et al. 1977). The predominantly agoraphobic sample of Mountjoy et al. (1977) did not improve significantly on agoraphobia or on depression, only on a social phobia scale; all these patients had, in addition to phenelzine, a daily dose of 15 mg diapezam and 10 mg nitrazepam, which confounds interpretation. In the agoraphobics of Lipsedge et al. (1973), iproniazid had a significant effect on phobic anxiety but not on phobic avoidance.

A report which has been omitted because it dealt with patients who had a diagnosis of primary depression of at least 4 weeks' duration, often with additional phobic symptoms, is that of Nies and Robinson (1981). These phobias accompanying depression responded to either phenelzine, 60 mg/day (but not 30 mg), or to amitriptyline, 150 mg/day.

Antidepressants are Broadly Patholytic, While Exposure is More Specifically Antiphobic and Anticompulsive

The patterns of antidepressant drug effects among different outcome measures are of considerable interest. In general, studies which found a significant drug effect for phobias or obsessive-compulsive phenomena also found a significant effect for depression (Ananth 1980; Insel et al. 1982; Marks et al. 1980; Mavissakalian & Michelson 1982; Pecknold et al. 1980; Sheehan et al. 1980). Exceptions are Zitrin et al. (1980) and Tyrer et al. (1973), where drug effect was present for phobias but not for depression and, in the case of Tyrer et al., not for panic either. It is relevant here that in anxiety disorders, too, imipramine was more effective than chlordiazepoxide or placebo in reducing depression as well as anxiety (Kahn et al. 1981).

When present in these syndromes, the drug-effect is not restricted to phobias, rituals, and anxiety-depression, but seems more general. In the few studies which report measures across a broad spectrum of different symptoms, antidepressant drugs seem to improve most measures in a pattern of *general patholysis*. As an example, Sheehan et al. (1980) found that imipramine and phenelzine patients improved significantly on every measure, regardless of whether it concerned phobias, anxiety, depression, hostility, interpersonal sensitivity, somatic, obsessive-compulsive or other scores. Marks et al. (1980) found the same general patholysis for rituals, depression, anxiety, and social adjustment (*see* their Table 3 and their Figures 2A and 2B). Similarly, McNair

and Kahn (1981) found an imipramine effect across a variety of problems such as panic, depression, and anger, though not for phobias (Table 4, modified from their Table 5). We do not yet know whether initial dysphoria is a better predictor of drug effect than is initial panic, anger, or hostility. Level of initial rituals or phobias has not been a good predictor where it has been examined.

Table 4

General Patholytic Effect of Imipramine in Agoraphobics Efficacy Summary for Completers at Week 8 (from McNair & Kahn 1981)

Criterion	Imipramine Effect	Imipramine X Depression	Imipramine X Phobic Severity
Agoraphobia-	.05	.05	
Phobic anxiety (SCL)	–	.05	.05
Panic	.05	–	–
Tension-anxiety (POMS)	.1	–	.05
Depression (SCL-self)	.05	–	–
" (SCL-Dr.)	.05	–	.01
" (POMS)	.1	–	–
" (Beck)	–	?	.05
Anger (SCL-self)	.001	.05	.001
" (SCL-Dr.)	.05	–	–
" (POMS)	.001	–	.01
Somatic (SCL-self)	.1	.1	.05
Global Improvement	–	–	.05

.05, .01, etc. = Significant on ANCOVA
– = Not significant

Given the general patholytic effect of antidepressant drugs on several aspects of distress like panic, free-floating anxiety, and depression, among others, all of which intercorrelate highly to the order of 0.60 or more, it might be misleading to concentrate on panic attacks as the focus of action, as some authors do (Sheehan et al. 1980; Zitrin et al. 1978, 1980). Undoubtedly imipramine can block panic attacks, but it also blocks a lot of other cohering pathological features simultaneously. It is illogical to accept any one of those features as primary unless and until detailed analysis has shown that change in that feature precedes change in the other aspects. This has not yet been done. Tyrer et al. (1973) found no improvement in panics despite improvement in phobias; ratings concerned symptoms over the previous 3 days. Zitrin et al. (1980) are the only ones to actually report measures of panic which improved along with phobias, and did not demonstrate that panic improves before phobias which sequence needs to be demonstrated if panic is to be regarded as the critical issue.

There is no reason to assume primacy of panics in agoraphobia. Panics are one of several manifestations of disturbed *mood*, others being free-floating background anxiety and depression, all of which tend to occur together. It is wise to heed the caution of McNair and Kahn (1981, pp. 77-78) that their "findings are not entirely congruent with Klein's views that relief of the agoraphobic component by imipramine is also independent of depression or that imipramine is ineffective for anticipatory anxiety. All of this underlines the need for greater knowledge of the role of depression, both secondary and primary, in the development and treatment of the panic-phobic syndrome."

It is of great interest to know why panics are so frequent in agoraphobia and in generalized anxiety disorder and unusual in obsessive-compulsive neurosis. A further issue is what differentiates anxiety disorders without agoraphobia from agoraphobic anxiety disorders. The question also arises why mood disturbance is so commonly associated with agoraphobia and obsessive-compulsive disorder.

The Diagnostic and Statistical Manual-III (DSM-III) subdivisions of dysthymic disorder, panic disorder, generalized anxiety disorder, and agoraphobia with and without panic attacks are not yet firmly based on hard scientific data showing that they have therapeutic or prognostic import. Symptoms of anxiety-depression (dysphoria) are a frequent feature not only in all these and in obsessive-compulsive disorder but also in many physical disorders, and are also the most common complaint in primary care populations across the globe. In one community survey "psychic distress," i.e., dysphoria, was present in 67 percent of agoraphobics (Balter, personal communication). The level of dysphoria may vary considerably among samples and partly account for differences in drug effects. Dysphoria from varied causes may be as responsive to antidepressants as is inflammation of diverse origins to aspirin, in both instances as long as the drug is given. We need to distinguish between drug effects on less specific features associated with a syndrome-like inflammation or dysphoria from

effects on more central features like bacteria in the tissues, or ritualistic or phobic behavior.

In contrast to the general patholytic action of antidepressants which tends to cease when the drug is stopped, the action of exposure treatment is both more specific and more lasting. Exposure therapy is only indicated where there is *persistent avoidance* of some discomforting situation or feeling. Exposure mainly improves rituals and phobias and, after a delay, work and social adjustment which had formerly been crippled by the rituals and phobias. This improvement continues over 2-7 years' followup (Marks, in press-a).

Despite its efficacy for phobias and rituals, exposure leads to a less impressive gain in mood, though this can become significant some time after phobias and rituals improve. Unlike drugs, behavioral treatment dissects apart the dual pathology in obsessive-compulsive and phobic patients. On the one hand, all of them have persistent rituals of phobias which can be specifically helped by exposure *in vivo*, and lastingly so, even though this has limited action on any coexisting dysphoria. On the other hand, in patients who have coexisting fluctuating dysphoria this is temporarily suppressed by antidepressants; as dysphoria improves do so coexisting rituals and phobias. While exposure treatment does not greatly modify disturbed mood, it protects against the reemergence of rituals and phobias in full strength when mood disturbance recurs; it uncouples the two pathologies (Marks 1981).

Are Any Antidepressants Especially Valuable?

Few comparisons are available. For ritualizers, clomipramine was effective in all four studies which used it (Ananth 1980; Insel et al. 1982; Marks et al. 1980; Thorén et al. 1980), but was not significantly superior to nortriptyline or amitriptyline. (Nortriptyline, amitriptyline, and clorgyline were each ineffective in one study (Ananth et al. 1980; Insel et al. 1982; Thorén et al. 1980). Antiphobic effects were found for imipramine in five (Mavissakalian & Michelson 1982; Sheehan et al. 1980; Tyrer et al. 1973; Zitrin et al. 1978, 1980) of seven studies (ineffective in Marks et al., in press; McNair & Kahn 1981), for phenelzine in two (Sheehan et al. 1980; Tyrer et al. 1973) of three studies (ineffective in Solyom et al. 1981), and for iproniazid (Lipsedge et al. 1973) and clomipramine (Pecknold et al. 1980) in one study each. For phobics between-drug comparisons are only available in one study, for phenelzine vs. imipramine (Sheehan et al. 1980); there was little to choose between them.

Problems of Drug Treatment

Relapse after drug withdrawal: In most of the phobic and obsessive-compulsive populations reviewed in this paper the disorder had been present for many years, often for more than a decade, by the time treatment began. In such chronic populations treatments are more valuable if their benefits last for years after the treatment ceases. This is true for exposure therapy but not, unfortunately, for antidepressants. Where a drug effect has been found, there is a uniformly high relapse rate on stopping the drug, even after it has been taken for 6-8 months. This is a drawback to drugs whose side effects over long periods are unclear. It indicates that the pathology is being suppressed rather than cured by such drugs, and there is a tendency for the mood disturbance to persist in a fluctuating manner for years. This finding contrasts sharply with the lasting improvement attributed to exposure treatments, which improved phobias and rituals up to the 2-9 years (reviewed by Marks, in press-a). The pattern of relapse following drug withdrawal, even after prolonged drug administration, is similar to that found with antidepressants in depressive illness, phenothiazines in schizophrenia, and cimetidine in duodenal ulcer.

High dropout rate with drugs in phobics: Another drawback to antidepressants is the high dropout rate found by almost all authors in phobics, these mostly from a quarter to a third (Lipsedge et al. 1973; Marks et al., in press; Mavissakalian & Michelson 1982; McNair & Kahn 1981; Sheehan et al. 1980; Tyrer et al. 1973; Zitrin et al. 1978, 1980). Interestingly, dropouts are common with placebo as well, suggesting that phobics are poor pilltakers. Often they interpret preexisting somatic complaints as drug side effects as soon as they start the drug. These misattributions are an interesting feature of the syndrome which deserve further study.

In contrast, the only three studies to report dropout rates with obsessive-compulsives found

these to be 4-14 percent (Insel et al. 1982; Marks et al. 1980; Thorén et al. 1980), comparing well with the 16 percent dropout rate for behavioral treatment as a whole in several hundred neurotic patients treated in the author's unit.

Implications for Research and for Clinical Practice

Future research studies could be better compared if they were to adopt a minimum number of standard measures. These might include a short Beck Depression Inventory and the Hamilton Depression Scale, target ritual or target phobia measures like those of Marks et al. (1980, 1982) and, for phobics only, the Fear Questionnaire of Marks and Mathews (1979) and panic scale of Zitrin et al. (1980).

Plasma monitoring of drug levels is desirable, and a followup for a minimum of a year after cessation of the drugs is essential to check on relapse. Also necessary is report of absolute mean scores, standard deviations, and cell size of each measure at each rating point from pretreatment to end of followup. Such data can be reported in one table taking up merely one journal page, and would greatly facilitate the task of comparing populations and effects across research centers.

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Medication in the Treatment of Panic Attacks and Phobic States

Donald F. Klein, M.D.[1]

Diagnostic Issues

In the now superseded Diagnostic and Statistical Manual-II (DSM-II) an anxiety neurosis was characterized by "anxious overconcern extending to panic and frequently associated with somatic symptoms. Unlike Phobic Neurosis, anxiety may occur under any circumstances." A patient with a phobic neurosis might show similar symptoms, but only when exposed to specific situations or objects, though these were consciously recognized as presenting no real danger.

Clinical research findings of the past two decades permit us to more precisely discriminate among anxiety and phobic conditions.

The crucial distinction is that the core event is the spontaneous panic attack, which may lead to the secondary development of anticipatory anxiety and tertiary phobic avoidances. That the panic attack is qualitatively distinct from, and not just an intensification of anticipatory anxiety, is supported by both the course of the disorders and differential pharmacological responses. Spontaneous panic attacks antecede the development of generalized anxiety rather than vice versa. Further, Klein (1964) demonstrated that the spontaneous panic attacks could be blocked by the tricyclic antidepressant imipramine which, however, did not affect anticipatory anxiety. Benzodiazepines and other minor tranquilizers, on the other hand, ameliorate anticipatory anxiety but have no marked effect on the panic attacks themselves. Thus, panic attacks appear to represent a form of anxiety biologically distinct from anticipatory (or "free-floating") anxiety.

This distinction leads to a more useful classification of anxiety and phobic disorders, separating those involving spontaneous panic attacks from those that do not. In DSM-III, the former are classified as Panic Disorder or Agoraphobia with Panic Attacks, depending on whether an individual with spontaneous panic attacks also develops a widespread inability to travel outside the home based in turn on fear of spontaneous panics. The attacks themselves are often episodic, and may clear for no apparent reason after 6-12 months. However, they tend to recur in volleys and occasionally become chronic. In addition, the agoraphobic avoidant and dependent behavior often becomes chronic because after a time the patient may give up trying to enter feared situations.

Other phobias that do not involve spontaneous panics are included in DSM-III as: Agoraphobia without Panic Attacks, Social Phobia, and Simple Phobia. Agoraphobia without Panic Attacks is, in the author's experience, regularly associated with episodic dysautonomic experiences; primarily light-headedness and gastrointestinal distress. Social Phobia is defined in DSM-III as a persistent, irrational fear of, and compelling desire to avoid, a situation in which the individual is exposed to possible scrutiny by others and fears that he or she may act in a way that will be humiliating or embarrassing. Examples of Social Phobia are fears of public speaking or performing in public, using public lavatories, eating in public, and writing in the presence of others. Simple Phobia involves an irrational fear of, and desire to avoid, specific, well-delineated, objects or situations not included in the definitions of Agoraphobia and Social Phobia. These often in-

[1]New York State Psychiatric Institute, New York, NY 10032.

volve animals, particularly dogs, snakes, insects, and mice, or situations such as closed spaces (claustrophobia) or heights (acrophobia). A trial of imipramine in Simple Phobia showed no specific benefit (Klein et al. 1980), as would be expected if the medication only affected spontaneous panics.

Physical disorders such as hypoglycemia, pheochromocytoma, hypercaffeinism, hyperthyroidism, and withdrawal from sedatives may cause symptoms similar to a panic attack and must be ruled out when making the diagnosis of Panic Disorder or Agoraphobia with Panic Attacks. These diagnoses are not made in DSM-III if the panic attacks are symptomatic of another mental disorder, such as Schizophrenia, Major Depressive Disorder, or Somatization Disorder

It may be a mistake not to diagnose Panic Disorder in the presence of major depressive disorder, since recent findings indicate that concurrent depression and Panic Disorder may have a higher degree of familial loading than depression alone (J. Leckman and M. Weissman, personal communication).

A number of features complicate the clinical picture and serve to obscure the diagnosis of Panic Disorder. Some patients manifest symptoms of depersonalization or derealization during a panic, which may also occur at times other than the panic attack. There may also be a relationship between separation anxiety in childhood and panic attacks, since between 20 percent (outpatients) and 50 percent (inpatients) of agoraphobic adults who come for treatment have a history of separation anxiety in childhood, often manifested as difficulty attending school (Klein 1964). It is noteworthy that imipramine has benefited school phobics refractory to psychotherapy in a controlled clinical trial (Klein et al. 1980).

Adult patients with Agoraphobia with Panic Attacks, who may present as housebound, desperately clinging, and fearful of being alone, have often been regarded as infantile personalities with severe, unmet dependency needs. The tendency has been to regard their symptoms as evidence of a failure to master the early stages of psychological development involving object constancy and separation-individuation. Long courses of psychoanalytic treatment were often prescribed which, in the light of recent findings, are not likely to be the treatment of choice.

Other complications of panic attacks are alcohol or sedative abuse. These may involve attempts at self-medication, which diminish anticipatory anxiety but have no effect on blocking panic attacks. Hence the dosages are often increased until physical or psychological dependence supervenes. An inquiry about antecedent panic attacks should always be included in the evaluation of alcohol- or sedative-abusing patients.

Panic attacks may also occur in conjunction with depressive illness (Pariser et al. 1979). At times the panic attacks may be the original symptom, with depressive complaints supervening. Most often this involves demoralization in response to the travel restrictions and attendant loss of self-esteem, and lacks many of the vegetative and autonomous mood disturbance features of a full-blown depressive syndrome. On the other hand, the illness may start with a major depression and be complicated by the subsequent development of panic attacks.

Several recent reports have also linked anxiety-panic syndromes to cardiovascular disorders such as hyperdynamic beta-adrenergic state (Easton & Sherman 1976; Frolich et al. 1969) and mitral valve prolapse syndrome (MVPS) (Pariser et al. 1979). While hyperdynamic beta-adrenergic circulatory state was originally described in patients who had attacks of palpitations, chest discomfort, or tachycardia after exercise or stress (Frolich et al. 1976), it has more recently been reported as brief episodes of nervousness or anxiety, often occurring without physical or emotional precipitants, that can be reproduced by isoproterenol infusions and blocked by maintenance propranolol (Easton et al. 1976). These findings suggest that some panic-attack patients may have increased beta-adrenergic receptor site reactivity.

Lactate Infusions and Panic Attacks

Patients with spontaneous panic attacks may have a pathophysiological aberration, since intravenous lactate infusions precipitate panic attacks in such individuals but not in normal controls (Pitts & McClure 1967).

This finding, established under double-blind circumstances, has been amply replicated by numerous investigators (Appleby et al. 1981;

Bonn et al. 1971; Fink et al. 1970; Kelly et al. 1971). It must be considered one of the better demonstrated facts in the experimental precipitation of psychopathological states. The meaning of this finding, however, still remains obscure. For instance, Pitts and McClure (1967) believe that the panicogenic effect was due to the chelation of calcium; they demonstrated that adding calcium to the sodium lactate mitigated the occurrence of panic attacks. Fink et al. (1970) replicated this finding.

Ackerman & Sachar (1974) raised the question whether there was truly a specific panicogenic effect from lactate. Perhaps some sort of conditioned response was responsible. During the lactate infusion autonomic symptomatology slightly reminiscent of the onset of the panic attack may occur which might engender a panic attack in patients, but not in normals who had not learned such a sequence.

Although possible, this hypothesis seems contradicted by several bodies of fact. First, EDTA infusions administered by Pitts (1967) produced profound hypocalcemic symptoms but no anxiety attacks in either anxiety neurotics or controls. Such infusions should certainly produce sufficient autonomic disturbance to throw patients into a panic attack if all that was required was a nonspecific trigger. Second, lactate-induced panic attacks resemble spontaneous panic attacks with regard to the blocking effects of antidepressants. Kelly's group (1971) induced panic attacks in eight agoraphobic patients and then treated them with phenelzine. Five of the eight patients responded well to the medication and did not have panic attacks upon reinfusion with lactate; the remaining three patients did not respond well to phenelzine and did reexperience panic attacks upon reinfusion with lactate.

More recently the author's research group has administered lactate infusions to 62 patients with Panic Disorder; 43 experienced panic attacks. After clinical recovery with imipramine, and while still on the drug, 28 were reinfused; only four showed evidence of a panic attack.

Even more telling, in a double-blind procedure 16 patients in remission from Panic Disorder were randomized to either continue on tricyclic antidepressants or to be withdrawn onto the peripherally acting anticholinergic drug, methscopolamine. After a month, they were reinfused with lactate. None of these patients panicked.

Pharmacotherapy

Tricyclic Antidepressants

That imipramine would block panic attacks (Klein 1964, 1967; Klein & Fink 1962; Zitrin et al. 1978) is of heuristic and practical importance. Agoraphobic patients with panic attacks had often been thought of as having a fear of open spaces or other specific situations, with long outpatient psychotherapies devoted to an exploration of unconscious sexual and aggressive impulses; the phobically barred areas were seen as symbols of forbidden temptations. Patients given imipramine report a dramatic decrease or cessation of panic attacks, however, many are still reluctant to change their phobic behavior patterns. Thus, persuasion, direction, support, or minor tranquilizers are often required, once the panic attacks had been blocked, to help patients extinguish their anticipatory anxiety which is not ameloriated directly by the tricyclic antidepressants, and to reenter the phobically avoided situations.

Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors are also effective in blocking panic attacks. Sheehan et al. (1980) recently reported a study in which phenelzine (45 mg/day) was at least as effective, if not more so, than imipramine (150 mg/day) in treating agoraphobics with panic attacks. That both major classes of antidepressants are effective in treating panic attacks should prove of marked heuristic importance.

Other Agents

In a detailed, thoughtful review of 16 controlled or partially controlled studies of beta-adrenergic blockers in anxiety disorders, Cole et al. (1979) concluded that this class of drugs may have a weak antianxiety effect. Specifically, the drugs often appear more helpful with somatic than with psychic aspects of anxiety. This conclusion was

also reached in a recent study by Noyes et al. (1980), who did a propranolol-placebo crossover study in patients with panic disorder. As such, it is useful for treating the anxiety symptoms that accompany the fear of public speaking and other social phobias. However, no controlled study has systematically examined the specific efficacy of propranolol in blocking panic attacks.

As mentioned before, minor tranquilizers are helpful in treating the anticipatory anxiety of Panic Disorder patients, but do not block the panic attacks. Preliminary findings of a controlled study by McNair and Kahn (1980) support this clinical impression. Panic attacks are also refractory to all classes of antipsychotic drugs, which may even exacerbate the condition. Because these patients are often considered borderline, and seen as decompensating when in acute panic, antipsychotics are often administered with a worsening of symptoms, use of more drug, further worsening, etc. leading to a vicious cycle (Klein 1962, 1964).

Hoehn-Saric et al. (1981) recently reported a double-blind, crossover placebo control study of clonidine in 23 patients. Nine patients were diagnosed as General Anxiety Disorder, and 14 as Panic Disorder. The period of active drug treatment was 2 weeks. The effect of clonidine was comparable in both anxiety disorders, and superior to placebo in patients who tolerated the drug. The main effect of clonidine was a decrease of anxiety attacks and psychic symptoms. No difference was found in the effectiveness of either drug for the two anxiety disorders. Hoehn-Saric (personal communication) reports a waning of clonidine beneficial effects with time.

An open pilot study of clonidine was conducted (Liebowitz et al., in press) in 12 patients with Panic Disorder. Only a third of the patients showed sustained improvement over a 6-week period. One third showed a transient improvement, which would have been registered as a positive course in Hoehn-Saric's (1981) 2-week trial, and a third was unable to tolerate the drug. Since clonidine also shows a waning of its inhibitory effect upon the locus coeruleus, this disappointing clinical finding may still be of marked theoretical importance.

A new drug, alprazolam (Xanax), a triazolobenzodiazepine with supposed antidepressant effects, may also be an antipanic drug. (Sheehan, personal communication).

Is the Antipanic Activity of Antidepressant Medication a Reflection of Antidepressant Effects?

Marks has recently completed a study of the imipramine treatment of agoraphobic patients and found no benefit from imipramine (Marks et al. in press). There are several problems with this study, including the dosage level attained and the statistical analysis. It is also not unusual for a Type II statistical error to occur in the study of active compounds; that is, not finding statistically significant effects when they, in fact, exist.

Marks, however, has suggested the alternative hypothesis that imipramine is only beneficial in the treatment of depressed agoraphobic patients and that the antipanic effect is actually part of a general patholytic effect. This line of thinking is supported by his findings in the chlorimipramine treatment of obsessive-compulsive disorder, where concurrent depression seemed necessary for beneficial drug effect. Marks also interprets a study by Thorén et al. as supportive of this viewpoint.

This is a controversial area. Marie Åsberg (personal communication) has disagreed with Marks' interpretation of this data. However, this discussion will be restricted to Marks' agoraphobia data, since there is no necessary parallel between drug effects on obsessive-compulsive disorder and agoraphobia.

Marks' handling of the term "depression" does not deal with the real difficulties in understanding just what different authors are referring to when they use this ambiguous word. In particular, the distinction of depression from demoralization seems crucial, since demoralization is a nonspecific response to many life defeats that manifests itself in depressive complaints. However, it is not generally considered to be a drug responsive depressive condition.

Marks has tabulated a number of studies where there are measures available that indicate that his sample, and the sample of Solyom et al. (1981) were relatively low in depression, and that this is consonant with his views concerning the essential role of depression in allowing therapeutic benefit. Unfortunately, the Solyom study is not good evidence, since the sample contains an unstated

proportion of social phobics, who are not generally considered drug sensitive. Therefore, Marks' study remains entirely alone in finding a lack of antidepressant benefit in agoraphobic patients.

When Zitrin and colleagues' study (1978) was compared to Marks' in terms of baseline depression measures, on the one measure where comparability was possible, there was no difference between samples. Further, in Zitrin's study there was no antidepressant effect of imipramine. This is not surprising, since in this study patients with more than moderate levels of depression, or with diagnosable major depressive disorder, were specifically excluded. Since there was no specific antidepressant effect, it is hard to see how an antidepressant effect could be a precondition for a therapeutic effect of imipramine in agoraphobic patients.

Marks points to the study of McNair and Kahn (1980) and of Sheehan (1980) where antidepressant effects were found as contradicting Zitrin's findings. However, in neither of these publications is there any indication that depressed patients were excluded from these studies. Further, in an analysis by Sheehan, no relationship was found between his measures of depression and antiphobic drug effect.

In the McNair and Kahn study (1981) there was a more complicated finding. Their results were analyzed for the 26 completers who were randomized to imipramine or chlordiazepoxide. They found that the imipramine effect on panic attacks was independent of degree of depression present in the sample. With regard to agoraphobia, that is avoidant behavior as a target, the best imipramine responders were the more depressed who were also more phobic. Because of the high correlation between degree of depression and phobia, these effects could not be statistically disentangled.

McNair and Kahn (1981) did not find a main imipramine effect on agoraphobia (avoidance behavior) but agreed that there was a definite effect on panic attacks. This finding is quite consistent with Klein's hypothesis that the initial antidepressant effect is blockading the panic attacks, and that the decrease in avoidant behavior is secondary. McNair's study lasted for only 8 weeks. This is a period that would allow for the development of antipanic effects, but would probably not have increased substantial secondary decreases in avoidance as indicated in the study of Zitrin et al. (1978).

Marks also discusses the possibility that antidepressants are broadly patholytic, while exposure is more specifically antiphobic. He asserts that drug effects are not restricted to phobias, rituals, and anxiety-depression, but seem more general. He supports this by referring to a group of univariate analyses which show many improvements with medication.

There are real methological problems with such an interpretation of multiple univariate contrasts. One does not know whether there is a general patholytic effect or whether there are a host of independent effects, or there is a central effect with a number of secondary beneficial reverberations. Finally, there may be a marked halo effect so that improvement in one area erroneously induces a perception of improvement in other areas. These methodological complexities are not alluded to. Further, other authors have shown a distinctly more spotty pattern of drug effects.

One problem is that it is not clear whether Marks is raising a strong hypothesis of general patholysis. If he is insisting that drugs always affect all symptoms, he is clearly wrong. If he is simply stating that drugs have effects on areas over and above phobias, anxiety, and depression, he is clearly right but the meaning of this remains to be elucidated.

Marks also states that it is misleading to focus on panic attacks since imipramine has effects on many other pathological features *simultaneously*. However, his data base does not allow this assertion of simultaneity.

Unfortunately the data regarding the effects of imipramine over an extended period of time are not definitive. The author's hypothesis that the effect is first upon panic attacks, and then secondarily upon anticipatory anxiety and avoidance has not been demonstrated in a longitudinal controlled way. It is quite consonant, however, with very extensive clinical therapeutic experience. It is also consonant with followup findings that relapse is initiated by the recurrence of spontaneous panic attacks. Finally, the blockade of lactate-induced panic attacks by antidepressants argues against considering the panic attack as just one more symptom.

Summary

The general question of the utility of medication in the treatment of Panic Disorder and Agoraphobia with Panic Disorder is reviewed. The utility of antidepressants is particularly striking. The claim that these beneficial effects depend upon the presence of concurrent depression with panic attacks, and that antidepressants have a general patholytic effect is critically examined.

Studies of the blockading effects of imipramine upon lactate-induced panic attacks also indicate a specific antidepressant-panic disorder interaction that is not related to depression.

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Agoraphobia: Behavioral and Pharmacological Treatments, Preliminary Outcome, and Process Findings[1]

Matig Mavissakalian, M.D.,[2] and Larry Michelson, Ph.D.[2]

Introduction

Within the last two decades agoraphobia has become well delineated as a syndrome in its own right (Hallam & Hafner 1978; Marks 1969; Snaith 1968), and this recognition has been coupled with the development of effective behavioral and pharmacological treatments (Mavissakalian & Barlow 1981a). The behavioral treatments which aim primarily to reduce phobic anxiety and avoidance share a common denominator, namely exposure to feared stimuli (Mavissakalian & Barlow 1981b). A number of analogues as well as clinical studies have demonstrated the superiority of *in vivo* exposure to imaginal exposure (Barlow et al. 1969a, 1970; Crow et al. 1972; Emmelkamp & Wessels 1975; Stern & Marks 1973). However, variations in the practice of *in vivo* exposure (e.g., prolonged exposure, successive approximations, therapist-assisted, home-based individual or group treatments), seem to be equally effective (Emmelkamp 1974; Emmelkamp & Ultee 1974; Everaerd et al. 1973; Hafner & Marks 1976; Hand et al. 1974; Mathews et al. 1977; Teasdale et al. 1977). New developments in the pharmacological treatment of agoraphobia have drawn attention to the antidepressant group of drugs, and numerous clinical studies have shown that both the monoamine oxidase (MAO) inhibitors (Kelly et al. 1970; King 1962; Mountjoy et al. 1977; Tyrer et al. 1973a, 1973b; Tyrer & Steinberg 1975) and the tricyclics (Colgan 1975; Klein 1964, 1967; Klein & Fink 1962; Marshall & Micev 1975; Sheehan et al. 1980; Waxman 1975; Zitrin et al. 1978, 1980) can be very effective.

To date, the literature does not permit definitive conclusions regarding the relative effectiveness of exposure and antidepressant treatments of agoraphobia, as controlled studies directly comparing these two treatments have not been reported. However, despite the existing methodological and assessment differences between studies cited above, certain overall similarities and differences emerge. First, it appears that dropout rates are comparable in behavioral and pharmacological studies and that they hover around 25 percent. Second, improvement rates are also comparable and center around 70 percent of treated patients. However, a major difference between these two treatments occurs in regard to relapse rate: Whereas improvement with exposure treatments is known to be maintained over long followup periods (Emmelkamp & Kuipers 1979; Marks 1971; McPherson et al. 1980), nearly 30 percent of patients experience relapse following cessation of antidepressants (Klein 1964; Klein & Fink 1962; Sheehan et al. 1980; Tyrer & Steinberg 1975; Zitrin et al. 1978, 1980). One of the major aims of this study, therefore, was to directly compare the effectiveness of *in vivo* exposure (flooding) and imipramine in the treatment of agoraphobia.

The literature suggests that antidepressants act by controlling or suppressing panic attacks (King 1962; King & Fink 1962; Klein 1964; Sheehan 1980; Zitrin 1978, 1980) and that exposure *in vivo*

[1]This research was supported in part by USPHS Grant MH-34177 from the National Institute of Mental Health.

[2]Department of Psychiatry, University of Pittsburgh, Western Psychiatric Institute and Clinic, Pittsburgh, PA 15213.

Reprint requests should be sent to Matig Mavissakalian, M.D., Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213.

may be the final common pathway leading to habituation or extinction of phobic anxiety and avoidance behavior (Mavissakalian & Barlow 1981b). It would follow that a combination of these two effective treatments with different mechanisms of action might prove maximally beneficial to the patient. Previous investigations of the combined behavioral-antidepressant treatment of phobias are rare, and until recently none had studied a homogeneous group of agoraphobics, nor had any study utilized exposure *in vivo*, the behavioral treatment of choice (Lipsedge et al. 1973; Solyom et al. 1973; Zitrin et al. 1978. The only exception is a study by Zitrin et al. (1980) comparing combined exposure-imipramine and exposure alone in 76 agoraphobic patients. They found that the majority of patients in both groups improved but that the combined treatment showed more improvement in panic and marked global improvement ratings. The second major aim of this study, therefore, was to directly compare the effectiveness of the combined flooding-imipramine treatment to that of flooding alone and imipramine alone.

Another major aim was the investigation of possible differential rates and patterns of change across the treatments. Because of the presumed differences in the mechanism of action underlying the effects of flooding and imipramine, and the possibility of an additive or synergistic effect in their combination, it was hypothesized that: 1) significantly greater change would be found earlier with the combined treatments than with the individual treatments, 2) mood, as measured by panic, anxiety, and depression, would improve earlier in treatment with imipramine than with flooding, 3) phobia and avoidance behavior would improve earlier in treatment with flooding as compared with imipramine and, 4) concordance between all measures of change would be greater in the later, rather than earlier phases of treatment due to desynchronous patterns of change, initially, across measures.

Finally, the question of nonspecific factors in psychiatric treatment is both a troublesome and a fascinating one. Troublesome, because if not properly isolated and controlled, far more credit will go to the presumed active therapeutic ingredients. Fascinating, because nonspecific factors could be looked upon as respectable treatments in their own right. In the special case of agoraphobia, practicing *in vivo* exposure between sessions seem to be the final common pathway for any successful treatment and it is possible, indeed likely, that a certain percentage of patients might improve with instructions, encouragement, and support by a therapist (Gelder et al. 1973; Jannoun et al. 1980; Mathews et al. 1976; McDonald et al. 1979). The third major aim of this study, therefore, was to assess the true effectiveness of the imipramine, flooding, and the combined imipramine-exposure treatments compared to a control group receiving nonspecific treatment.

In 1980 a clinical research program was established at Western Psychiatric Institute and Clinic at the University of Pittsburgh to investigate flooding and imipramine treatments in 80 agoraphobic patients. This paper reports the results of the first 32 subjects who entered the project.

Method

Subjects

The 32 subjects of this study were selected on the basis of the following inclusion criteria: 1) Diagnostic and Statistical Manual-III (DSM-III) diagnosis of Agoraphobia, 2) age of onset prior to age 40, 3) duration of present illness of at least 1 year, 4) a score of 4 or greater on the clinician rating of global assessment of severity, and 5) failure to complete either the standardized behavioral test or the idiosyncratic behavioral test or completing both behavioral tests while experiencing definitive anxiety (a rating of 4 or more on a 0-8 scale of anxiety). Exclusionary criteria were: 1) presence of features indicative of and/or previous diagnosis of Major Affective Disorder, Schizophrenia, Organic Brain Syndrome, and Obsessive-Compulsive Disorder, 2) social phobics and anxiety neurotics without the typical fears of going out alone to open spaces, streets, shops, crowds, cars, and means of public transport, and 3) presence of physical illness precluding the use of imipramine either because of the illness itself or because of treatment necessary for that illness. Additionally, patients selected for the study were withdrawn from psychotropic medications at least 2 weeks prior to initiation of treatment. This selection process eliminated 27 diagnosed

agoraphobics. The main reasons for their rejection, in decreasing order, were mild condition, physical or medical problems, and refusal to take experimental medications.

The 32 patients had a mean age of 39 years. There were 5 males and 27 females: 2 were single, 3 divorced, and 27 married. The majority were white with only 2 blacks. The average duration of illness was 14 years. Ninety-one percent of the patients had received previous psychiatric treatment of an average duration of 22 months. Eighty-seven percent of the patients had received anxiolytic medication, 32 percent had received antidepressants, and none had been prescribed antipsychotics. Only 16 percent of the patients had been previously hospitalized.

Six patients did not complete the treatment phase. All of them were females. One patient withdrew after two sessions because she was hospitalized with gynecological problems for possible hysterectomy. Two patients attended two sessions each but quit because they preferred to return to conventional group therapy. One patient withdrew after one session because of difficulty in arranging transportation to the clinic. The last two patients missed several sessions in a row and were disqualified. Additionally, three patients discontinued drugs within the first 2 weeks of treatment but completed the entire treatment phase. For the purposes of data analysis, they were reassigned to the placebo (no medication) group. Thus, the final composition of the groups was as follows: Imipramine/Flooding—five patients, Imipramine—six patients, Flooding—six patients, and Nonspecific treatment—nine patients.

Treatment Conditions and Design

The experimental design of the study is a 2 × 2 factorial design with eight patients randomly assigned to each of the four following treatment conditions: Group IF (combined treatment group) consisted of patients receiving 1) imipramine; 2) 90-minute group flooding; and 3) individual 15-minute therapeutic instructions. Group I (imipramine treatment group) consisted of patients receiving 1) imipramine; 2) 90-minute group discussion; and 3) individual 15-minute therapeutic instructions. Group F (flooding treatment group) consisted of patients receiving 1) placebo; 2) 90-minute group flooding; and 3) individual 15-minute therapeutic instructions. Group NS (nonspecific treatment group) consisted of patients receiving 1) placebo; 2) 90-minute group discussion; and 3) 15-minute individual therapeutic instructions. The entire treatment phase consisted of 12 weekly sessions.

Drug Treatment

Patients were assigned to either imipramine or matched placebo according to a predetermined randomization order known only to the hospital pharmacist. Thus, drug treatment was double-blind. In the weekly individual sessions, one tablet of imipramine 25 mg or placebo was prescribed at bedtime and increased by 25 mg increments every second day until a tolerable maintenance dosage or a maximum of 200 mg (8 tablets) was reached. The average maintenance dosage of imipramine attained in the last month of treatment was 119 mg per day (range 25-200 mg) and that of placebo was 166 mg (range 50-200 mg).

Behavioral Treatment

In addition to the individual sessions, patients, in groups of eight, were assigned alternatingly to either flooding or discussion conditions. In the flooding condition, they were encouraged to enter their most phobic situations either alone or with the assistance of the therapist at first. This typically involved going to the center of town, visits to department stores and shopping malls, bus rides, and walking in congested areas alone uninterruptedly for longer and longer distances. The patients assigned to the group discussion met with the same therapist for general discussion of their phobias and their progress. Instructions and reinforcement for self-controlled *in vivo* practice were repeatedly given, and general practical suggestions such as engaging the help of a friend or spouse and/or selecting certain specific phobic situations for that particular week's practice were offered. However, specific cognitive strategies such as paradoxical intention or self-statement training were not given. The mean number of sessions attended by the patients was 11.

Therapeutic Instructions

All patients were given the same therapeutic rationale and instructions. Briefly, they were told that the reason why their fears had continued and even increased with time was due to their habitual avoidance behavior, and that in order to overcome their fears and anxieties they should stop avoiding and start entering their phobic situations. It was strongly suggested to them that once in a phobic situation, they should remain there and tolerate the anxiety-discomfort until it decreased to fairly comfortable levels and/or until their urge to escape abated (i.e., habituation took place). They were also told that it is a good principle to proceed with their self-controlled exposure practices along a hierarchy from the least to the most phobic situations. Their progress was reviewed weekly, reported gains in improvement were reinforced, and patients were encouraged to proceed with their self-controlled *in vivo* practices. Furthermore, it was emphasized to them that whatever additional treatment they received, such as the drugs and the group treatments, was designed to facilitate their carrying out self-controlled *in vivo* exposure practices.

Therapists

The same psychiatrist (MM) saw all the patients in the weekly 15-minute individual sessions, and the same clinical psychologist (LM) conducted the group sessions.

Assessment

A comprehensive assessment battery consisting of clinical ratings of severity of illness, general symptom checklist, clinical ratings of phobia, anxiety, panic, and depression as well as direct measures of agoraphobia in behavioral, subjective, and physiological response systems was administered at pretreatment, at 4, 8, and 12 weeks of treatment, and at 1 month posttreatment. The rationale for using these numerous measures was to enable subsequent and more detailed psychometric and clinical analyses of their inter- and intrarelationships. The authors are currently examining these widely used outcome measures in regard to both internal consistency (i.e., Kudar-Richardson 21 reliabilities, factor analysis, and item analyses), and external validity (i.e., discriminant, convergent, concurrent, and predictive).

Results

Repeated measures analysis of variance (ANOVAS) were performed across pre-4-8-12 weeks and 1 month posttreatment assessments and between the four experimental conditions, as presented in Table 1, and indicated significant main effects, repeated measures effects, and interaction effects on numerous dependent measures.

Table 1

Repeated Measures analysis of Variance on Measures Showing Significant Difference Among Imipramine-Flooding (IF), Imipramine (I), Flooding (F), and Nonspecific Treatment Groups (NS) Post-Hoc Comparisons Using Newman-Keuls Tests Between Treatment Groups

Measure	Group	Pre $\bar{X}$	4 $\bar{X}$	8 $\bar{X}$	12 $\bar{X}$	1 Month $\bar{X}$	Main Effects *F*-Ratio	Repeated Measures *F*-Ratio	Interaction Effects *F*-Ratio	4th Week	8th Week	12th Week	1 Month Post-treatment
SRS	IF	7.3	4.0	3.8	2.0	1.8	3.21[a]	55.54[c]	1.65	NS[a]	NS	1234	2314
	I	6.2	3.6	3.0	2.2	0.8							
	F	6.8	4.0	3.6	2.4	1.4							
	NS	7.2	4.8	5.4	4.0	4.8							
HSCL	IF	101.6	(—)	(—)	63.8	61.4	5.49[b]	31.73[c]	0.86	(—)	(—)	2314	2314
	I	80.8			52.8	55.4							
	F	95.8			60.8	57.3							
	NS	107.0			79.4	91.4							

Table 1 (Continued)

	IF	88.8	85.2	80.2	75.6	79.6							
	I	88.5	78.0	72.8	70.6	76.6							
MHQ	F	87.8	81.2	78.7	76.5	73.0	3.33[a]	22.07[c]	1.23	NS	NS	2134	NS
	NS	85.3	86.3	82.7	85.0	87.6							
	IF	82.2	61.8	51.2	31.0	31.4							
	I	67.0	39.6	34.4	39.6	28.0							
FQ-T	F	57.3	33.8	31.2	26.2	18.8	3.11[a]	40.76[c]	4.24[c]	NS	3214	3214	1324
	NS	62.0	61.3	56.5	52.0	62.5							
	IF	7.4	4.0	3.6	1.8	1.2							
	I	7.8	4.6	3.4	2.3	1.6							
PAA	F	7.3	4.8	3.6	2.5	1.4	3.43[a]	102.16[c]	2.76[b]	NS	NS	123 4	132 4
	NS	7.4	6.0	4.9	4.6	4.9							
	IF	21.0	12.6	16.6	14.6	15.2							
	I	19.0	12.2	10.6	8.6	9.2							
MAS	F	23.2	15.2	12.3	10.7	7.7	4.78[b]	15.83[c]	1.91[a]	231 4	231 4	2314	3214
	NS	21.0	21.0	20.2	18.0	19.2							
	IF	5.6	3.0	2.4	2.5	2.0							
	I	3.8	1.5	2.3	1.0	0.7							
Panic	F	5.7	3.0	1.2	0.8	0.6	3.37[a]	11.77[c]	0.91	NS	NS	NS	3214
	NS	6.3	4.6	5.7	2.7	4.3							
	IF	18.0	12.0	7.0	7.2	5.4							
	I	15.0	5.8	2.4	1.4	1.8							
BDI	F	12.2	7.5	6.8	4.3	4.8	3.27[a]	24.97[c]	0.90	231 4	NS	2314	2314
	NS	20.0	13.0	9.6	10.8	13.0							
	IF	58.6	46.8	44.6	41.6	43.2							
	I	50.6	39.8	43.2	32.3	32.2							
SDS	F	56.2	46.7	39.8	41.7	40.0	3.54[a]	10.71[c]	1.22	NS	3214	2134	2314
	NS	55.8	52.2	58.0	49.0	53.6							
	IF	3.1	1.6	2.1	0.3	0.4							
	I	2.2	3.3	2.3	1.6	0.8							
S-SUDS	F	3.6	3.5	3.0	0.5	0.5	3.15[a]	9.73[c]	1.01	NS	NS	1324	1324
	NS	4.8	4.0	3.1	2.8	3.2							

[a] $p < .05$ [b] $p < .01$ [c] $p < .001$ [d] (NS = Not significant)

NOTE: (—) = No data for that assessment phase.

Abbreviation used:

SRS = Self-Rating of Severity
HSCL = Hopkins Symptom Checklist
MHQ = Middlesex Hosp. Question.
FQ-T = Fear Questionnaire-Total
SDS = Zung Depression Scale
MAS = Taylor Manifest Anxiety Scale
PAA = Phobic Anxiety and Avoidance
Panic = Panic Scale
BDI = Beck Depression Inventory
S-SUDS = Mean Subjective Unit of Discomfort During Behavioral Course

Outcome Analyses

Two (medication vs. placebo) × two (flooding vs. discussion) analyses of covariance were performed on all major dependent measures at the 1 month posttreatment assessment. The results, as presented in Table 2, show significant main effects, medication effects, flooding effects, and interaction effects for the vast majority of the measures. Indeed, there were significant main effects across all domains of functioning including severity of illness, phobia, anxiety, depression, and behavioral measures of phobic anxiety and avoidance. In regard to medication effects significant findings were also obtained within each of these above domains. Similarly, flooding effects were pronounced across all domains, except for the two depression measures. As can be seen in Table 2, significant interaction effects were also obtained on all but two measures.

After obtaining statistically significant main effects, the four experimental groups were compared using Neuman-Keuls posthoc analyses (a Table 1). The results indicated that th nonspecific (NS) control group was significant less effective than the other three treatments. I deed, the NS group evidenced statistically signifi cant weaker therapeutic effects on 10 majo dependent measures across all domains of fun tioning. However, as can be seen in Table there were no significant differences between th imipramine and the flooding groups. Furthe more, no significant differences were found be tween the combined treatment (IF) and its in dividual components. These results sugge equivalency across the flooding, imipramine, an combined treatments.

Next, a series of clinically oriented analys were performed based on operationally define measures of improvement and end-state functio ing. Table 3 shows that at 1 month posttreatme assessment, 73 percent of the patients had im proved highly and 58 percent were functioning a high level.

Table 2

2 × 2 Analyses of Covariance Between Combined Imipramine-Flooding, Imipramine, Flooding, and Nonspecific Treatment Conditions

Major Dependent Measures at 1 Month Posttreatment	Main Effects *F*-Ratio	Medication Effects *F*-Ratio	Flooding Effects *F*-Ratio	Interaction Effects *F*-Ratio
Severity/General Symptomatology				
Global Assessment of Severity (GAS)	8.00[b]	13.10[b]	4.08[a]	<1
Self-Rating of Severity (SRS)	7.50[b]	9.09[b]	5.91[b]	13.46[b]
Hopkins Symptom Checklist (HSCL)	5.61[b]	4.37[a]	7.12[b]	8.39[b]
Middlesex Hospital Questionnaire (MHQ)	2.67[a]	<1	5.26[b]	<1
Phobia				
Fear Survey Schedule (FSS)	<1	<1	<1	—
Fear Questionnaire—Total (FQ-T)	15.11[c]	13.19[c]	21.53[c]	9.03[b]
Fear Questionnaire—Agoraphobia (FQ-Ag)	13.43[c]	11.48[b]	15.15[c]	3.32[a]
Phobic Anxiety and Avoidance (PAA)	9.61[c]	8.67[b]	11.35[b]	9.07[b]
Anxiety				
Zung Self-Rating Anxiety Scale (SAS)	6.37[b]	2.80[a]	10.49[b]	3.32[a]
Taylor Manifest Anxiety Scale (MAS)	1.57	<1	3.08[a]	20.13[c]
Panic Scale	3.57[a]	<1	6.67[b]	12.39[c]
Depression				
Beck Depression Inventory (BDI)	4.01[a]	7.28[a]	<1	6.41[a]
Zung Self-Rating Depression Scale (SDS)	2.01	3.82[a]	<1	7.86[a]
Behavioral Measures				
Standard Course Battery (S-BAT)	<1	<1	<1	—
Subjective Unit of Discomfort S-SUDS	7.58[b]	4.18[a]	9.40[b]	4.58[a]
Idiosyncratic Behavioral Test (I-BAT)	1.72	3.44[a]	<1	—
Subjective Unit of Discomfort I-SUDS	8.05[c]	7.23[b]	7.83[b]	6.06[a]

[a] $p < .05$ [b] $p < .01$ [c] $p < .001$

Table 3

Improvement and End-State Functioning at the 1-Month Posttreatment Assessment

Number of Criteria Met (Maximum-4)	Improvement		End-State Functioning	
	N	%	*N*	%
0	2	8	5	19
1	3	12	2	8
2	2	8	4	15
3	11	42	6	23
4	8	31	9	35

Chi-squares were then performed to compare patients scoring low (0-2) vs. those scoring high (3-4) on improvement and end-state functioning across the four experimental treatment conditions. The results were statistically significant (improvement: Chi-square = 14.14, 4 *df*, $p < .01$, ETA = .74; end-state: Chi-square = 17.26, 4 *df*, $p < .001$, ETA = .81) and revealed that the three active treatments were superior to the NS group. Indeed, none of the active groups had cases of low improvement in contrast to the NS group where the majority of patients (e.g., 75 percent), evidenced a low level of improvement.

Finally, the presence (+) or absence (−) of spontaneous panic attacks (SPA) was assessed. At pretreatment, 69 percent of the patients were SPA (+), while at 1-month posttreatment this had declined to 27 percent. Furthermore, interesting differences emerged between the four experimental conditions. Sixty percent of the patients in the IF group were SPA (+) at pretreatment, which declined to 0 percent at 1-month followup. The figures were identical, pre-50 percent and 1-month followup 17 percent SPA (+), for both the I and F conditions. In the NS group, 75 percent were SPA (+) at pretreatment and this had declined to only 50 percent at 1 month followup.

Process Analyses

To ascertain during which assessment phase(s) significant changes occur, sequential *t*-tests were performed comparing pre-4, 4-8, 8-12, and 12 weeks-1 month posttreatment segments in the overall group and within each experimental condition.

Table 4 presents the results which reveal that significant changes occur early on many measures and that there is a reduction in the number of measures reaching significance in subsequent phases of treatment. It is interesting to note that in the first month of treatment, 11 out of the 14 measures achieved significant changes with the combined treatment. The same effect was obtained with imipramine, whereas only seven measures reached significance with flooding. The notable difference between I and F were measures of anxiety and depression. Furthermore, four of the central measures of agoraphobia also show significant improvement with the nonspecific treatment in the first month of treatment, supporting the therapeutic usefulness of providing rationale and instructions to agoraphobic patients.

The second and third months of treatment seem to be a period of consolidation of gains, with fewer measures reaching significance. This would suggest that with the active treatments, major gains occurred in the first month of treatment, with improvement continuing to occur up to 1 month posttreatment. Interestingly, measures of agoraphobia as well as depression and performance improved significantly in the second month of treatment even with the nonspecific treatment. However, little change occurred after this period with this treatment, suggesting that its effectiveness is limited to the initial phase of the intervention.

In contrast, significant improvement on measures of phobia and anxiety continued to take place with flooding in the posttreatment phase. This would suggest that patients treated with flooding continue their treatment, on a self-directed basis, thus consolidating gains after formal termination of therapy. In addition, the imipramine group, far from relapsing, seems to experience further reduction in the severity of their agoraphobic condition.

Table 1 also illustrates the Neuman-Keuls posthoc comparisons of the experimental treatment conditions at each assessment. Two comparisons at Week 4 reached significance, indicating that the imipramine condition alone was superior to the control treatment on clinical anxiety and depression measures. However, there were no significant differences between the three active groups. By Week 8 the three active treatments still did not differ significantly, although im-

ipramine and flooding treatments differed significantly from nonspecific treatment on a clinical anxiety measure and flooding, in addition, differed significantly from the nonspecific group on a depression measure. At the 12-week assessment, and at the 1 month posttreatment assessment, the three active treatments did not differ significantly from one another but achieved significantly greater results compared to the nonspecific group on most measures.

The Figure illustrates these differential patterns of change and underscores the marked and rapid improvement in mood which imipramine induces and which is apparent by Week 4. It also shows that similar changes occur with flooding but that this treatment may require up to 8 weeks to equal the changes seen with imipramine. On both measures of anxiety and panic, rate of improvement levels off with imipramine between 4-8 weeks of treatment, whereas improvement maintains a steady pace with flooding. Moreover, improvement in depression is rapid and equivalent for both imipramine and flooding treatments in the first month. Further improvements continue with both treatments, albeit more gradually with flooding. Finally, on the measure of agoraphobic anxiety and avoidance, the course of improvement with both treatments is identical. Interestingly, improvement in subjective anxiety experienced during the behavioral avoidance test does not improve in the first 4 weeks of treatment except with the combined imipramine/flooding treatment. This is puzzling, because in the same period flooding remains unchanged and imipramine induces a worsening on this measure. Furthermore, this apparent advantage of the combined group is lost by Week 8. On this measure, and in contrast to the other measures of mood, major changes seem to occur in the later phases of treatment and appear to be associated more strongly with flooding.

Table 4

Sequential T-Test Comparisons of Pre-4-8-12 Weeks and 1-Month Posttreatment Assessments for Overall Sample, Imipramine and Flooding, Imipramine, Flooding, and Nonspecific Control Conditions

	GAS	SRS	HSCL	MHQ	FSS	FQ-T	FQ-AG	PAA	SAS	MAS	PANIC	BDI	SDS	S-BAT	S-SUDS	I-BAT	I-SUDS
Pre to 4	IF O	IF F O I NS	(—)	IF F O I	IF F O I	IF F O I	IF F O I NS	IF F O I NS	O I	IF O I	O I F NS	IF O I	IF O I	O	IF	(—)	(—)
4 to 8	IF O F		(—)	O I	I		O	F O I NS	F	O	F	O NS			O NS	(—)	(—)
8 to 12	O NS	IF O I	IF O F NS		IF	O	IF O I	IF O I		O			O I		O F	I O	IF F O
12 to One Month Post		I	NS sig. worsening			F	F	O		F							I

Note: Presence of group code indicates statistically significant differences between the previous assessment phase and the assessment where the code appears
O = Overall Group
I = Imipramine Group
IF = Meds/Flooding Group
F = Flooding Group
NS = Placebo/Discussion Group
(—) = No data for these measures at 4-and 8-week assessment
($p < .05$)

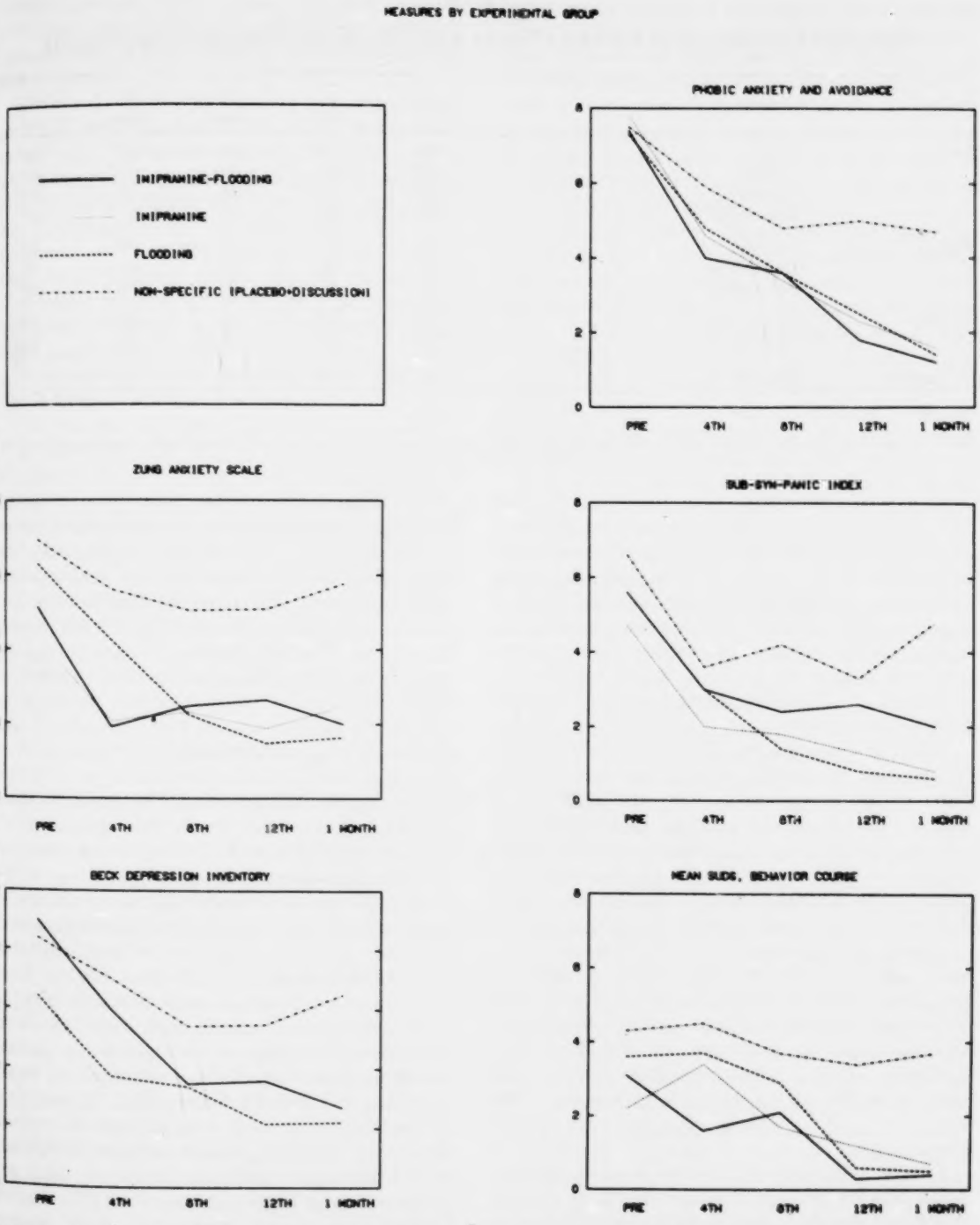

FIGURE. Measures of anxiety, depression, phobic anxiety and avoidance, panic, and distress during the behavioral course across the four experimental treatment conditions.

Table 5

Canonical Correlations at Pre-4-8-12 Weeks and 1-Month Posttreatment Assessments

Domain I	Domain II	Pre	4th Week	8th Week	12th Week	1 Month Post
Severity	Phobia	.89[c]	.87[a]	.91	.97[a]	.92[a]
	Anxiety	.82[a]	.80	.95	.95[a]	.89[a]
	Depression	.84[b]	.74	.80	.76	.84[a]
	Behavioral	.56	.78[a]	.91	.97[c]	.92[b]
Phobia	Anxiety	.69	.68	.98	.86	.89[b]
	Depression	.63	.79	.72	.80	.70
	Behavioral	.51	.58	.95	.95	.95[c]
Anxiety	Depression	.53	.84[a]	.85	.90[b]	.79[b]
	Behavioral	.73[a]	.69	.66	.81	.75
Depression	Behavioral	.46	.19	.55	.83	.74

[a] $p < .05$ [b] $p < .01$ [c] $p < .001$

Note: The size of the correlation needed to achieve statistical significance may differ across assessments due to varying sample sizes. Thus, the absolute leve correlation in addition to the resultant significance level, should be considered.

Next, multivariate canonical correlation analyses were performed to evaluate the patterns of relationship between the different domains of assessment in the course of treatment. Based on hypothesis of differential rates and patterns of change across treatments and measures earlier in treatment, the authors expected to find low correlations among the various domains earlier in treatment, and higher correlations in the later phases of treatment.

Table 5 presents the domains, their constituents, and the results of the canonical correlations at all assessments. The results depict a steady increase in the percent of domains correlating significantly as well as a parallel rise in the strength of the correlations as treatment progresses. These results strongly support the idea of differential rates and patterns of change across measures occurring in the early phases of treatment and justify further explorations in regard to the phenomena of synchrony/desynchrony and concordance/disconcordance across treatments and domains, as discussed by Hodgson and Rachman (1974). Moreover, these results add support to the use of multiple process/outcome measures with which to delineate these phenomena.

Finally, patients were divided into two groups, depending on whether they met 0-2 (LEF) or 3-4 (HEF) of the end-state functioning criteria (*see* Table 3) and compared across each assessment phase. The results of the *t*-tests showed no pre treatment differences between HEF and LEF pa tients. However, by Week 4, significant di ferences emerged on many of the major depen dent measures, in favor of the HEF group. Th pattern continued at Week 8, and by the 12-wee assessment showed increases strength in regard t both the number and size of the differences.

Discussion

The degree of improvement found in the entir sample reflects the overall effectiveness of th clinical research project. Despite the inheren methodological constraints (nine patients receive nonspecific control treatment), the overall level o improvement compares favorably with previously reported outcome studies with imipramine o flooding (Mavissakalian & Barlow 1981a). Thu the magnitude of change on the clinical scales (2- point decrease on 9-point scales are considere marked improvement in the literature), the con sistent statistical significancy obtained on nearl all measures, and the finding that 73 percent o the patients witnessed a high level of improve ment with nearly 60 percent enjoying a high leve of functioning, all indicate that the research pro gram was also highly therapeutic. The author believe this is an important point becaus agoraphobic patients, like most chronically

disabled groups, enter clinical research projects with great expectations of being helped—which it appears were in great measure fulfilled in the current project.

The results show that flooding and imipramine are highly and equally effective in the treatment of agoraphobia. Although was found partial support for the hypothesis predicting earlier improvement in mood with imipramine, mood was also found very responsive to flooding and the two treatments did not differ from Week 8 of treatment onward. These results suggest the exercise of extreme caution in attributing an exclusive etiological treatment status to pharmacotherapy which purportedly would treat the core problem of "endogenous anxiety" in agoraphobia (Sheehan et al. 1980).

The results did not support the hypothesis which predicted that phobic avoidance and anxiety would improve earlier with flooding. In fact, there was suggestive evidence that anxiety, experienced during the behavioral testing, improved in the later phases of treatment, even in those patients treated with flooding. In a recent study, (Mavissakalian & Michelson, in press) which investigated differential rates and patterns of change between the three response systems of behavioral performance, subjective anxiety, and physiological responsiveness measured by heart rate, it was found that clinical and behavioral improvement occured early in treatment followed by improvement in subjective anxiety and heart rate in the intermediate and later phases of treatment. These results were interpreted as supporting the hypothesis advanced by Hodgson and Rachman (1974) predicting that psychophysiological improvement would lag behind behavioral improvement in flooding or similar behavioral treatments with high demand characteristics. Such high demand characterized the treatment of all the patients who were repeatedly instructed to practice self-directed flooding. The increased concordance between all domains of assessment in the later phases of treatment adds further support to the predictions of change advanced by Hodgson and Rachman concerning treatments with high demand characteristics.

A major and unexpected finding was the failure of the combined imipramine flooding treatment to show a clear superiority over the individual treatments. *Therefore, when therapeutic rationale and instructions to practice in vivo exposure are given to patients, it appears that imipramine, flooding, or their combined treatment are highly and equally effective in the short-term outcome of agoraphobia.* This finding raises serious questions as to the need for combined treatments in agoraphobia and suggests that the primarily clinical advantage stemming from the combined treatment would be the possibility of reduced relapse rates, compared to pharmacotherapy alone. The prolonged followup phase planned in the completed research project will address this question. However, preliminary findings of a 6-month followup reported by Zitrin et al. (1980) are not encouraging since they revealed that 27 percent of agoraphobic women treated with combined imipramine and flooding relapsed, a figure which is as high as those encountered with antidepressants alone (Sheehan et al. 1980).

Therapeutic rationale and instructions to practice *in vivo* exposure, even though systematically prescribed over a 3-month period, seem to be inadequate by themselves. In this condition, some improvement seems to take place in the first 8 weeks of treatment but subsequently levels off. This contrasts with the marked improvement noted in the earlier phases as well as the continuing improvement in the later phases of active treatments, and suggests that this is a weak and time-limited treatment. However, the observation that two out of the nine patients in this group showed high levels of improvement suggests that in a small percentage of agoraphobics these nonspecific treatment factors can be sufficiently effective in their own right and, furthermore, that in this weaker treatment certain patient characteristics might prove crucial in determining substantial degrees of improvement.

In regard to the differential patterns of change between low end-state and high end-state functioning patients, it was observed that more rapid treatment gains occurred among the high end-state functioning group. Indeed, these patients were already showing significant improvement by the 4th week and continued to accelerate their therapeutic responses across subsequent assessment phases. Conversely, the low end-state functioning group showed significantly slower and smaller treatment gains. These findings suggest that early changes in treatment could be extremely useful in identifying responders, and that clini-

cians might incorporate these findings into their treatment by considering alternative interventions for patients who fail to show gains by Weeks 4 or 8. On the other hand, pretreatment baseline measures did not differ between responders and nonresponders and therefore do not seem likely to provide prognostically helpful information at this time.

If the completed projects' results confirm these preliminary findings, it would raise the question and search for a common factor to explain the similarity of outcome between the active treatments. Since all patients in all groups received the same therapeutic rationale and instructions to practice, it is conceivable that the degree of self-practiced exposure is a major mediating factor in these treatments. If this is truly the case, one would expect to find less practice in the nonspecific group than in the other three treatment groups which, in addition, would not differ significantly in this respect. The authors plan to examine the role of self-directed practice in the various treatments, using continuous naturalistic data collected by means of diaries.

In summary, these preliminary results indicated that imipramine, flooding, and their combination treatment are equally effective in the treatment of agoraphobia, given that rational and basic instructions to practice *in vivo* are present. Clearly, these findings need replication on larger samples. Likewise, the numerous questions raised, relating to both process and long-term outcome, require further elucidation. What seems likely, however, is that self-help groups relying solely on discussion and providing support and information as well as instructions to face phobic situations may be of limited effectiveness in the treatment of chronic agoraphobia.

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Comparison of Generalized Anxiety Disorder With Panic Disorder Patients

Rudolf Hoehn-Saric, M.D.[1]

Few attempts were made to distinguish subgroups of patients with the broad diagnosis of "anxiety neurosis" prior to the reclassification of anxiety disorders in the Diagnostic and Statistical Manual-III (DSM-III). The discovery that antidepressants prevent the reoccurrence of panic attacks but do not affect anticipatory anxiety (Klein 1981), led to the division of anxiety neurosis into panic disorder and generalized anxiety disorder. Several studies have investigated panic disorders (Klein et al. 1978; Mountjoy et al. 1977; Sheehan et al. 1980), however, the description of generalized anxiety disorders in DSM-III was based on clinical impression rather than on systematic data. In an earlier study, Hoehn-Saric (1981) reported that generalized anxiety disorder patients differed from those with panic disorders mainly in physical symptoms. Generalized anxiety disorder patients also rated themselves more introverted than those with panic disorder. Recently, a survey which examined symptomatic volunteers found those who were diagnosed as having panic disorder rated themselves nigher on the anxiety subscale and the panic anxiety subscale of the Hopkins Symptom Checklist than volunteers who were classified as generalized anxiety disorder (Barrett 1981). This paper presents a more extensive comparison between the two disorders, based on a multi-axial approach, which describes state measures, personality measures, social adjustment, and disturbance during childhood.

[1]Johns Hopkins School of Medicine, Baltimore, MD 20205.

Method

Subjects

The population consisted of 133 patients who were admitted to the Anxiety Clinic at the Johns Hopkins Hospital. All patients suffered persistent anxiety for at least 6 months, had no history of psychotic disorder, were not substance abusers, and were sufficiently educated to rate various questionnaires. Criteria for panic disorders followed the guidelines of DSM-III; however, it included patients who experienced panic attacks only once a month. Patients who had experienced panic attacks in the past but, in spite of lack of adequate treatment were free of panic attacks for at least 6 months, were placed in the category of Generalized Anxiety Disorder.

Of the 133 patients examined, 48 percent were diagnosed Generalized Anxiety Disorder and 52 percent Panic Disorder. The average age was 33.9 years, ranging between 18 and 58. Eight-two percent were white and 18 percent black, 60 percent female and 40 percent male, 45 percent were married and the others were single, separated, or divorced. The average education was 13 years, with 8th grade as minimal education. There were no significant differences on any of the demographic data between the two diagnostic conditions.

Measures

At the time of admission to the Anxiety Clinic, patients filled out four types of questionnaires

overing present state (symptoms), personality raits, social and personal adjustment, and ehavioral disturbances during childhood. The ollowing measures were employed:

State Measures

Physician Ratings. 1) *Hamilton Anxiety Scale* (Hamilton 1959): This scale describes psychic and somatic symptoms associated with anxiety. 2) *Global Rating of Generalized Anxiety:* A 4-point scale describing the general level of anxiety. 3) *Global Rating of Anxiety Attacks:* A 4-point scale describing sudden emergence of anxiety, including panic attacks. 4) *Global Neurotic Scale:* A 4-point scale rating psychic symptoms of anxiety. 5) *Global Somatic Scale:* A 4-point scale rating physical symptoms of anxiety.

Patient Ratings. 1) *State- Trait Anxiety Inventory, State Form* (Spielberger et al. 1970): This form describes the present level of psychic anxiety. 2) *Affects Balance Scale* (Derogatis 1975): A self-rating scale of four positive and four negative affects. 3) *Somatic Symptoms Scale* (Hoehn-Saric 1981): Describes somatic symptoms that frequently accompany anxiety. 4) *Zung Scale of Depression* (Zung 1965): Describes symptoms associated with depression.

Personality Measures

1) *Eysenck Personality Questionnaire Form A* (Eysenck & Eysenck 1975): Measures two personality dimensions: extraversion, which describes the person's sociability and impulsivity, and b) neuroticism, which measures trait anxiety, dysphoria, and lability. 2) *Mastery-Powerlessness Scale* (Frank et al. 1978): This modification of Rotter's Locus of Control Scale (Rotter 1966) rates the person's perception of internal control, i.e., the degree to which he is in control of himself and his environment, as opposed to external control, i.e., seeing himself at the mercy of fate and other forces. 3) *State-Trait Anxiety Inventory, Trait Form* (Spielberger et al. 1970): This scale describes a person's general tendency to respond to anxiety.

Social Adjustment

Clark Personal and Social Adjustment Scale (Clark 1968): This scale appraises the effectiveness and satisfaction at work, interpersonal relationships, feeling of optimism, and feeling of mastery.

Childhood Behavior Disturbance Measure

Childhood History (Tarter et al. 1977): This is a 50-item checklist of behaviors associated with children diagnosed as "minimal brain disorder."

Statistics

Student's *t*-tests were used to compare the differences between scale values in Generalized Anxiety Disorder patients from those of Panic Disorder patients. In addition, discriminant analyses (Wilks) were calculated to identify items differentiating the two disorders.

Results

Table 1 summarizes the differences between the Generalized Anxiety Disorder and Panic Disorder groups. Patients with a Panic Disorder rated significantly higher on the total score of the Hamilton Anxiety Scale ($p < .005$) and, as expected, on the Global Rating of Anxiety Attacks ($p < .001$). The reason that patients diagnosed as Generalized Anxiety Disorder also scored on anxiety attacks was due to the vagueness of the scale which included not only panic attacks, but also strong, rapidly increasing fluctuations of anxiety levels. Ratings on the Zung Scale of Depression and the Global Rating of Generalized Anxiety failed to discriminate between the two groups. Additionally, none of the psychic subscales discriminated significantly between the two groups. However, all of the somatic scales, including the somatic subscale of the Hamilton Anxiety Scale ($p < .001$), the Global Somatic Scale ($p < .003$), and Somatic Symptoms Scale ($p < .05$), differentiated between the two groups. None of the personality measures, the social adjustment ratings, or the Childhood History differed between the two disorders.

Symptoms of the Somatic Symptoms Scale were subdivided into classes describing muscular symptoms, symptoms associated with hyperventilation, cardiovascular symptoms, and gastrointestinal and genital symptoms. Only symptoms

Table 1

Comparison of Generalized Anxiety Disorder With Panic Disorder Patients

		Generalized Anxiety Disorders	Panic Disorder	Signific
STATE MEASURES				
General Scales				
Hamilton Anxiety Scale	67[a]	19.8 ± 7.1	25.0 ± 7.0	.00
Global Ratings of Generalized Anxiety	129	1.8 ± 0.7	1.6 ± 0.9	.10
Global Ratings of Anxiety Attacks	129	1.2 ± 1.1	2.0 ± 0.9	.00
Zung Scale of Depression	131	56.5 ± 14.5	58.1 ± 13.4	-
Psychic Subscales				
Hamilton Anxiety Scale, Psychic Subscale	67	11.2 ± 4.0	12.1 ± 3.5	-
Global "Neurotic" Scale	104	2.5 ± 0.8	2.7 ± 0.9	-
STAI, State Form	134	52.0 ± 14.8	56.0 ± 12.00	.10
Affects Balance Scale	133	0.04 ± 1.1	-0.28 ± 0.9	.10
Somatic Subscales				
Hamilton Anxiety Scale, Somatic Subscale	67	8.7 ± 4.4	13.2 ± 4.9	.00
Global "Somatic" Scale	104	2.1 ± 1.0	2.6 ± 0.9	.00
Somatic Symptoms Scale	133	19.2 ± 12.7	23.7 ± 11.4	.05
SOCIAL ADJUSTMENT				
Clark Scale	113	31.7 ± 8.0	33.4 ± 9.0	-
PERSONALITY INVENTORY				
Eysenck Personality Questionnaire	116			
Extraversion		9.5 ± 4.1	9.6 ± 4.5	-
Introversion		16.3 ± 4.9	16.9 ± 4.5	-
STAI, Trait Form	121	51.8 ± 11.3	54.8 ± 11.1	-
Mastery-Powerlessness Scale	112	13.2 ± 4.4	12.2 ± 4.3	-
CHILDHOOD DISTURBANCES				
Childhood Scale	107	7.4 ± 6.2	9.1 ± 6.6	-

[a]Number of patients with completed scales

associated with hyperventilation and the cardiovascular system differentiated significantly between the two disorders ($p < .05$ for each symptom subclass). On individual physical symptoms, patients with panic disorder rated significantly higher ($p < .05$ or higher) on the following subscales: fatigue, sweating, heart pounding, difficulty breathing, having a lump in the throat, headaches, attacks of irritability, attacks of depression, and lower degree of vigor.

Table 2 outlines the results of the discriminant analysis. Only patients with complete records were included. The Hamilton Anxiety Scale, which was introduced after collection of half of the population, was excluded from the analysis. Since highly correlated items are automatically eliminated from the discriminant analysis, the state form of the State-Trait Anxiety Scale wh correlated with the Zung Depression Sc ($r = 0.69$, $p < .001$), does not appear on Table The analysis discriminated to a significant deg between the two disorders ($p < .001$). The analy indicated that in addition to physical sympto the lack of positive affects, the presence negative affects, and general "neurotic" sy toms, differentiated between patients with pa disorders and generalized anxiety disorders. discriminant analysis of the subscales of Somatic Symptoms Scale (*see* Table 3) confirm that symptoms associated with the cardiovascu system and hyperventilation also differentia the two groups ($p < .04$). Furthermore, insom and loss of sex drive were strongly represented the Panic Disorder patients.

Table 2

Generalized Anxiety Disorder vs. Panic Disorder Discriminant Analysis (Wilks) $N = 87$, (GAD:43, PD:44)

Standardized Canonical Discriminant Function Coefficients:	
Zung Depression Scale (PD higher)	1.25
Affects Balance Scale, Total Positive (PD lower)	1.00
Physicians' Ratings of Anxiety Attacks (PD higher)	−0.68
Affects Balance Scale, Total Negative (PD higher)	−0.59
Global Neurotic Symptoms Scale (PD higher)	0.49
STAI, Trait Form (PD higher)	−0.47
Physicians' Ratings of Generalized Depression (PD higher)	0.45
EPI, Extraversion (PD higher)	−0.36
Physicians' Ratings of Irritability Attacks (PD higher)	−0.36
Physicians' Ratings of Generalized Anxiety (PD lower)	0.34
Global Somatic Symptoms Scale (PD higher)	−0.26
Somatic Symptoms Scale, Muscular Symptoms (PD higher)	−0.24
Group Centroids	
Generalized Anxiety Disorder	0.89
Panic Disorder	−0.87

Canonical discriminant function: Wilks lambda 0.55, $df = 12$, sig. = 0.000

Table 3

Generalized Anxiety Disorder vs. Panic Disorder Discriminant Analysis of Items of the Somatic Symptoms Scale (Wilks) $N = 124$ (GAD: 60/PD: 64)

Standardized Canonical Discriminant Function Coefficients:[a]	
Tingling in arms and legs	0.57
Difficulties sleeping	0.57
Loss of sex drive	−0.57
Heart pounding or racing	−0.51
Sweating	−0.48
Headaches	−0.43
Group Centroids:	
Generalized Anxiety Disorder	−0.35
Panic Disorder	−0.32

[a] Panic disorder group rating higher on all symptoms

Canonical discriminant function: Wilks lambda 0.90, $df = 6$, sig. = 0.04

Discussion

The study confirmed previous findings that patients with Panic Disorder diagnosis score higher on somatic, but not on psychic anxiety scales than patients with a Generalized Anxiety Disorder diagnosis (Hoehn-Saric 1981). In addition, it was demonstrated that the groups differed predominantly in symptoms describing hyperventilation and cardiovascular changes rather than symptoms relating to the muscular and gastrointestinal systems. The results also showed that Panic Disorder patients tend to experience more negative affects, such as depression and irritability. The extended survey failed to replicate the previous finding that Generalized Anxiety Disorder patients are more introverted (Hoehn-Saric 1981). Moreover, the extraversion dimension of the Eysenck Personality Questionnaire correlated poorly with the other measures ($r = \leq .35$), indicating a weak relationship to psychopathology. The neuroticism dimension of the Eysenck Scale was significantly correlated with all psychic scales, the Zung Depression Scale, and the Somatic Symptoms Scale ($r = .43$ to $.69$, $p < .001$), but failed to differentiate between the two diagnostic groups.

The lack of relationship between the diagnostic categories and personality variables, social state, and childhood history suggests that the primary difference between patients who develop panic attacks and those who experience generalized anxiety may lie in their physical response to stress. However, an examination of the population suggests that patients with the diagnosis of Generalized Anxiety Disorder may form a heterogeneous group. Some patients who had experienced panic attacks in the past changed into having generalized anxiety without further panic attacks, while other patients who had suffered from generalized anxiety for years eventually developed a panic disorder. The latter sequence has also been reported by Cloninger et al. (1981). Moreover, in a previous study, Hoehn-Saric and Masek (1981), discovered a group of patients who corresponded to the description of Generalized Anxiety Disorder except that they lacked autonomic hyperactivity. These patients had a significantly higher degree of forehead muscle tension than normal controls. However, heart rate and skin conductance remained comparable to the control

group. A pilot study, which the investigator is conducting at the present time, suggests that within moderate degrees of anxiety, some patients experience pronounced autonomic symptoms such as increased diastolic and systolic blood pressure, while others exhibit pronounced muscular symptoms without excessive cardiovascular changes.

Further investigations will be necessary to determine if patients with a Generalized Anxiety Disorder constitute a continuum whose symptoms relate directly to the severity of anxiety, or if they represent distinct subgroups with different constitutionality, one being autonomically labile and the other autonomically stable. If this should be the case, one would expect that under sufficient stress the autonomically labile group would develop panic attacks, while the autonomically stable group may exhibit various psychic symptoms, insomnia, and somatic symptoms associated with increased muscle tension, but would not develop a panic disorder. A dichotomy of patients diagnosed as Generalized Anxiety Disorder into those with high and low levels of cardiovascular symptoms was not helpful, because patients who scored high on cardiovascular symptoms also rated high on all other psychic and somatic measures. Thus, it appears that patients with high levels of anxiety experience all types of somatic symptoms. This does not exclude the possibility of a distinct subgroup of anxiety disorders which, due to their greater autonomic stability, remain within moderate levels of anxiety ratings. A clarification of the existence of such subgroups will be of importance in the pharmacotherapy of anxiety disorders.

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Unresolved Issues in the Treatment of Agoraphobia With Panic Attacks

Michael R. Liebowitz, M.D.,[1] and Donald F. Klein, M.D.[1]

There is at present considerable confusion in the treatment for agoraphobia regarding the respective roles of various forms of psychotherapy and medication. A number of self-help phobia groups specifically eschew the use of medication. Even groups (Chambless 1981) who recognize the utility of antidepressant medication first recommend extensive, complex courses of psychotherapeutic treatment and consider medication only if such treatment fails. A literature review to determine the relative utility of pharmacological and behavioral forms of treatment and the specific impact of each upon the various components of the agoraphobic syndrome reveals the need for further comparative trials.

As defined in the Diagnostic and Statistical Manual-III (DSM-III), Panic Disorder is a condition characterized by the sudden and unprovoked occurrence of severe anxiety which can border on terror, and which is usually accompanied by such symptoms as palpitations, breathlessness, sweating, faintness or dizziness, nausea, or diarrhea. The attacks usually last only 20-30 minutes, but become the source of great concern to patients who fear they are going crazy, having a heart attack, or about to lose control of themselves in some socially embarrassing way. What usually follows is the development of great anticipatory anxiety, which is often treated or self-treated with tranquilizers or alcohol. A third stage involves phobic avoidance of places where panic attacks typically occur or where rapid exit to seek help is difficult, such as public transportation, heavy auto traffic, bridges, tunnels, restaurants, theaters, churches, or crowded stores. When a widespread, disabling avoidance pattern becomes established, the patient meets DSM-III criteria for Agoraphobia with Panic Attacks.

Pharmacotherapy

The pharmacotherpay of panic attacks has advanced greatly in the past two decades. Of major importance was the recognition that panic attacks, although not the accompanying anticipatory anxiety, could be effectively blocked by the tricyclic antidepressant imipramine, but not by minor tranquilizers such as the benzodiazepines (Klein & Fink 1962; McNair & Kahn 1981). On the other hand, benzodiazepines but not tricyclics appeared to be effective for the anticipatory anxiety that often develops as a consequence of panic attacks. This led Klein to hypothesize that panic attacks and non-panic anxiety represent two distinct pathophysiological entities. However, a recent report (Lipman et al. 1980) that non-panic chronic anxiety states also respond preferentially to tricyclics over benzodiazepines, and that the benzodiazepine alprazolam may effectively block panic attacks (Sheehan 1982); suggests that further studies are required before firm boundaries between panic anxiety and non-panic anxiety conditions are drawn.

Extending these findings were studies that demonstrated that the monoamine oxidase inhibitors (MAOI) were also highly efficacious for

[1]College of Physicians and Surgeons, Columbia University and New York State Psychiatric Institute, New York, NY 10032.

panic attacks (Tyrer et al. 1973). Phenelzine was also shown to block the ability of sodium lactate to precipitate panic attacks in Panic Disorder patients (Kelly et al. 1971), a phenomenon also recently demonstrated for imipramine by the authors' research group. The ability of sodium lactate to induce severe anxiety attacks in patients vulnerable to spontaneous episodes but not in normal controls was first demonstrated by Pitts and McClure (1967) and later replicated by several other investigative groups (Fink et al. 1969) including work done by the authors.

A recent double-blind, placbo-controlled study comparing the efficacy of the tricyclic imipramine and the MAOI phenelzine in patients with panic attacks found both drugs to be highly effective with a trend to superiority for phenelzine (Sheehan et al. 1980). One problem that limits the generalizability of these findings is that dosages of both active drugs used in the study were fixed and low, phenelzine being limited to 45 mg/day and imipramine to 150 mg/day, while in the authors' experience some panic patients require phenelzine doses of up to 90 mg/day or imipramine doses of 300 mg/day or more.

Behavior Therapy

Paralleling the progress in clinical psychopharmacology was the recognition that many agoraphobic individuals could be markedly helped by behavior therapy, coupled with a gradual refinement of those techniques. The modern era of behavior therapy of phobias actually dates back to the late 1950s with Wolpe's reports of the use of systematic desensitization, which involved having patients go through an imagined hierarchy of fear-producing situations while practicing deep muscle relaxation (Wolpe 1958). A variant of this technique developed by Stampfl and called imaginal flooding, has patients begin by imagining themselves confronting their most feared situation rather than slowly building up from non-feared situations as Wolpe had them do (Stampfl 1970).

While much debate occurred over the actual therapeutic mechanisms of these behavioral techniques, a central principle of all therapists who treat phobias is that to overcome the fear a patient must actually confront phobically avoided objects or activities. Given this, beha therapists began to wonder if it did not m more sense to directly try systematic densensi tion or flooding in live situations rather tha imagination. From this evolved several *in viv* posure techniques (prolonged exposure, cessive approximations, therapist-assis homework assignments, individual or group) a variety of investigators in short-term stud have found to be more quickly effective than posure in imagination for treating agoraphobic well as simple phobics (Mathews et al. 1981). the studies by Zitrin et al. (1978, 1980) expos *in vivo* was faster-acting but did not improv greater proportion of the patients than ot techniques over 26 weeks.

Pharmacotherapy vs. Behavior Therap

With the emergence and proven efficacy of t easily applied treatment techniques, one ph macological and the other behavioral, the n question to be asked was: "How do these t forms of treatment compare with each other i patients with panic attacks and agoraphobi Recently, several studies have attempted answer this question, but a number of import issues have not been satisfactorily resolved.

One study by Solyom et al. (1981) compar phenelzine and exposure in a 2 × 2 double-bli design involving 40 patients who were eith agoraphobic or socially phobic. Phenelzine w given for 6 weeks in doses up to 45/mg day, wh exposure appears to have involved therapist i structions for patients to confront anxiety-eliciti situations bolstered by three telephone calls p week to the patient. Patients who did not rece exposure were not "systematically encouraged confront phobic situations."

While the authors concluded that exposur with or without phenelzine, was the superi treatment, there are a number of issues whi limit the generalizability of this conclusion. One that, as acknowledged by the authors, phenelzi doses of 45 mg or less are below the 60-90 mg lev now found effective with depressed patient Secondly, 6 weeks of medication treatment much less than the 26 weeks found optimally e fective for agoraphobics in other studies (Solyo

t al. 1981; Zitrin et al. 1980). Thirdly, social hobics, who have not generally shown to be esponsive to antipanic medications, are mixed in with agoraphobics without separate pretreatment tratification or even independent reporting of the esults. Also, no mention is made about how nany patients in either group had spontaneous panic attacks; while most agoraphobic patients do, this is not always the case. For this reason, DSM-III distinguishes between Agoraphobia with Panic Attacks and Agoraphobia without Panic Attacks. Finally, one might reasonably argue that the investigators in this study are not comparing clinically meaningful modes of treatment. Pharmacologists familiar with treatment of phobias will tell their patients that in addition to taking medication they must push themselves to confront feared situations; where they differ in practice from behavior therapists is by not offering a structured program to bring this about. The clinically relevant comparison is how drugs plus such informal "exposure instructions" compare to formal exposure programs without drugs, and the Solyom study cannot answer this question.

At approximately the same time Zitrin et al. (1980) reported a study of 76 agoraphobic women randomly assigned to imipramine or placebo while all received group *in vivo* exposure for a 10-week period. Medication was started first; from weeks 5-14, patients received one exposure session per week lasting 3 hours. Medication was continued until week 26; the maximum possible dose of imipramine was 300 mg.

This study found imipramine plus exposure superior to placebo plus exposure at both 14 and 26 weeks in terms of clinical global improvment, primary phobia, and spontaneous panic. Interestingly, the active drug group continued to improve between weeks 14 and 26. At 26 weeks the imipramine patients tend to be markedly improved, while more placebo patients tended to register moderate improvements, although some were also markedly improved. (According to the independent evaluator, 62 percent of imipramine patients were markedly improved on clinical global ratings at 26 weeks, while 28 percent were moderately improved and 10 percent showed no or only minimal improvement; for the placebo group, 29 percent were markedly improved, 42 percent moderately better, and 29 percent only minimally better or unimproved.) An interesting finding was that panic attacks increased between weeks 14 and 26 (after discontinuation of exposure) in the placebo but not in the active drug groups. Given these findings, it makes sense that future studies should extend the drug treatment period to 26 weeks, far beyond the usual 6 to 8 weeks. It also makes sense now to try extending the exposure treatment period to 26 weeks as well, since a once-weekly group session for 6 months is not an impractical form of clinical treatment.

While the dropout rate was the same for the two treatment groups (29 percent), eight of twelve active drug dropouts left because of a refusal to take medication, while only one could not keep up with the exposure program. For the placebo group, three of ten refused to continue medication, while five of ten were unable to keep up with the group. Whether dropouts (and nonresponders) unwilling to comply or unable to benefit from one type of treatment would do well with the other is an open question.

At 6 months posttreatment, 27 percent of the imipramine and 6 percent of the placebo group had relapsed. While these differences were not statistically significant, they have been cited by other investigators to show that drug treatment is less durable, even when combined with exposure. However, the data can be looked at another way, namely, that a certain percentage of agoraphobics require continued medication to maintain their gains, and will relapse when medication is withdrawn even after 6 months of treatment.

This study also found that the more depressed patients were at the beginning of treatment, the worse they did, which weighs against Marks' argument that imipramine's effect is confined to agoraphobics with associated depression (Marks et al., unpublished). Zitrin et al. (1978, 1980) believe that the dysphoria often seen in agoraphobics is symptomatic of antidepressant unresponsive demoralization rather than tricyclic responsive endogenous depression, since they found no drug specific antidepressant effect. Scientific progress since the time the Zitrin et als.'s study was begun now allows investigators to also distinguish signs of frequently associated atypical depression (Liebowitz et al. 1981) in agoraphobic or panic patients. On the basis of preliminary evidence, panic patients with associated atypical depressions may not do particularly well on tricyclics (Liebowitz et al. 1982).

Zitrin et al. had earlier reported a 26-week study comparing systematic desensitization plus imipramine, systematic desensitization plus placebo, and supportive psychotherapy plus imipramine in 218 patients (Zitrin et al. 1978). Diagnostically the patients were divided into agoraphobics, simple phobics, and mixed phobics (who had circumscribed phobias, panic attacks, and no travel restrictions). Overall, imipramine was found superior to placebo in the agoraphobic and mixed phobic groups in reducing overall severity of illness, improvement in phobias, reducing severity, and frequency of panic attacks and reducing other anxiety symptoms, while no differences were found between behavioral and supportive psychotherapy for any diagnostic group. In addition, for the agoraphobic group ($N = 77$), behavior therapy plus imipramine was clearly superior to behavior therapy plus placebo in reducing the frequency and severity of anxiety attacks, as measured by the Acute Panic Inventory and the Taylor Manifest Anxiety Scale, for the travel and panic symptom clusters on the Wolpe-Lang Fear Survey Schedule, and for independent evaluators rating of primary phobia improvement.

Marks and colleagues also recently compared imipramine (up to 200 mg/day for 28 weeks), placebo, therapist-aided exposure, and therapist-aided relaxation for 45 agoraphobic patients in a 2 × 2 design (Marks et al., unpublished). All patients were given systematic self-exposure homework including an instruction manual. No significant effects were found for imipramine, while significant but limited effects were found for therapist-aided exposure. Marks et al. concluded that self-exposure homework is a powerful therapeutic device, that imipramine adds nothing for agoraphobics who are not depressed, and that therapist-aided exposure is helpful for some patients.

One limit on the generalizability of Marks' conclusions is low medication dosages; mean doses were 124 mg at Week 6, 158 mg at Week 14, and not reported at Week 26. (Mean drug plasma levels were in the antidepressant range, but inflated by several outliers.) In addition, a number of patients previously shown not to respond to antidepressants were taken into the study. Also, among the patients counted as dropouts were two who showed rapid improvement with imipramine. One other interesting point was that
patients were put on imipramine during the ad
treatment followup period, including 8 who h
been on imipramine before. However, no me
tion is made as to whether these individua
deteriorated when taken off medication the fi
time.

However, comparison of Marks' sample se
ratings of "feeling blue" are almost identical wi
the Zitrin-Klein sample; therefore, the differen
in drug effects is unlikely to be due to lesse
depression in Marks' sample. Further, Zitri
Klein specifically barred acceptance of any pa
tient with diagnosable depression.

Mavissakalian and Michelson (1981) hav
recently reported the preliminary results of a
ongoing comparison of imipramine, placeb
flooding, and nonspecific psychosocial treatme
in agoraphobic patients using a 2 × 2 design. Al
patients were given weekly therapeutic instructio
on the importance of trying to enter fear situa
tions. Maximum imipramine dose was 200 m
and duration of treatment was 12 weeks. The con
trol for *in vivo* exposure was a group discussion o
illness and progress. Patients previously treate
with antidepressants were not excluded; in fact
all 32 patients reported in the pilot study ha
previously received antidepressants of some typ
although drug dosage, duration, and previou
response are not indicated. Average dose of im
ipramine in the last month of treatment was 12
mg/day. A behavioral performance test was use
as an outcome measure, as was an overall judg
ment about degree of improvement.

What is reported are the results obtained at
month posttreatment. Both imipramine and ex
posure were found to be active treatments, wit
no significant differences between them and n
additional benefits seen in the combined group
No predictors are offered as to which patients d
well with one or another form of treatment
although the investigators speculated that im
ipramine may stabilize mood (block panic?
which leads to behavioral change, while *in vivo* ex
posure may produce behavioral and then mood
improvement.

Conclusion

What are needed are drug versus exposur
studies that exclude patients previously show

ıresponsive to either test treatment, use of adeıate doses and duration of medication, continue posure treatment for patients who respond, test nresponders for their responsivity to other rms of treatment, and rigorously evaluate both pe and degree of associated depression. opefully, this will generate clinical predictors of ho responds best to pharmacological or ehavioral treatment of agoraphobia. Among the ecific hypotheses that require testing are the llowing:

1. That patients whose panic attacks are in mission or on the wane but who still have high nticipatory anxiety will do well with group *in vivo* xposure without accompanying drug treatment.

2. That patients with severe or frequent ongog panic attacks will do better with antipanic rug treatment, and may become more phobic or emoralized if treated with an *in vivo* exposure rogram unaccompanied by drug treatment.

3. That patients with frequent or severe panic nd high anticipatory anxiety may require both orms of treatment but will do better if drugs are ffered first, to be followed by a formal exposure rogram once panic attacks are blocked.

4. That some of the agoraphobic patients who mproved with exposure, unaccompanied by lrug, may overcome their phobic avoidance but till continue to experience panic attacks that they ıave now learned to tolerate or "float through." This could be assessed by self-report, by *in vivo* physiological monitoring, and by pre- and posttreatment challenges with sodium lactate infusions to test changes in panic vulnerability.

5. That many agoraphobic patients will respond to drug treatment without any concomitant psychotherapy except simple encouragement of self-exposure. This has never been examined in a formal study; previous trials of antidepressant medication in agoraphobics that have employed adequate dosage and duration of treatment have embedded these trials within various forms of psychotherapy. Thus, it remains unclear whether psychotherapy is necessary to help patients reduce anticipatory anxiety and avoidant behavior once panic attacks have been blocked by medication. Clinical anecdotal evidence indicates that many patients can rid themselves completely of the agoraphobc syndrome by simple drug treatment accompanied by encouragement of self-exposure activity (Muskin & Fyer 1981).

6. That depressive features are not necessary for imipramine's anti-panic effects and, in the case of associated atypical depression, may impede it. On the other hand, demoralization may impede self-exposure and extinction of anticipatory anxiety.

7. That imipramine's principal effect in agoraphobia is to block panic attacks, and that the lessening of anticipatory anxiety occurs after the antipanic effects. This could be assessed by having patients keep daily logs and ratings of frequency and intensity of episodes of panic and anticipatory anxiety as well as frequent investigative assessments of both types of symptomatology.

The authors now have in hand two relatively effective modes of treatment for Agoraphobia with Panic Attacks, but further comparative trials are required before they can fully identify the mechanisms by which each works, or say which is preferable as a first try for any particular patient.

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Antiobsessional and Antidepressant Effects of Clomipramine in the Treatment of Obsessive-Compulsive Disorder

Thomas R. Insel, M.D.,[1] Ina Alterman, M.A.,[1] and Dennis L. Murphy, M.D.[1]

Two treatments for obsessive-compulsive disorder (OCD) have recently been demonstrated to be effective. A particular form of behavior therapy using exposure and response prevention techniques has prompt and lasting effects for OCD patients who ritualize (Foa & Goldstein 1978; Marks et al. 1980). Pharmacologic treatment, in particular, treatment with clomipramine, has also been shown to be effective, although less information is available about the magnitude and duration of the effects (Insel & Murphy 1981; Thorén et al. 1980). One promising aspect of clomipramine treatment is that patients without rituals or avoidant behavior and patients with secondary depressions, i.e., groups for whom behavioral interventions may be less effective (Foa 1979), may be drug responders. Whether all categories of obsessional patients are likely to respond to clomipramine remains controversial. For instance, Marks (1981) has recently noted, after reviewing several studies, that clomipramine was less effective for nondepressed OCD patients in one study than in comparable studies using somewhat more depressed OCD patients.

The authors attempted to evaluate both antiobsessional and antidepressant effects in an ongoing double-blind study of clomipramine, clorgyline, and placebo for OCD. While much of the data from this study have yet to be analyzed, a preliminary comparison of a few rating scales yielded data pertinent to the following questions: Do baseline depression ratings in OCD patients predict response to clomipramine? Are changes in obsessional and depression rating scale scores correlated during clomipramine treatment? Are the time courses for antiobsessional and antidepressant changes different and, if so, which effect occurs first?

[1]Clinical Neuropharmacology Branch, National Institute of Mental Health, Bethesda, MD 20205.

Method

The authors studied 12 OCD patients, fulfilling Diagnostic and Statistical Manual-III (DSM-III) criteria and Research Diagnostic Criteria (RDC) and including both ritualizers and pure obsessionals at the Clinical Center of the National Institutes of Health. The patients (age 19-45, mean 29.9 years) included seven males and five females. The double-blind study involved crossover trials of clorgyline and clomipramine, although only clomipramine results were analyzed for this report (trend effects within the crossover were not significant). Daily clomipramine dosage ranged from 100 to 300 mg (mean 220 mg). The following clinical ratings were scored for this analysis: Hamilton Depression Scale (18 items) (Hamilton 1967); the Comprehensive Psychiatric Rating Scale-Obsessive compulsive (CPRS-OC) subscale, (Thorén et al. 1980); the CPRS-OC subscale modified to include only primary obsessional symptoms (compulsive thoughts, rituals, concentration difficulty, indecision, lassitude); and global assessment scale for depression and obsessions (each requiring a single number rating

between 1 (no symptoms) and 15 (maximum symptoms). These ratings were completed at least every 2 weeks and in many cases weekly. Not all patients had the same rater, although each patient had the same rater throughout the study. The authors calculated percent clinical response by comparing scores at the end of 6 weeks on drug with baseline values (i.e., the end of 4 weeks on placebo).

Results

The entire sample improved after 6 weeks of clomipramine treatment with mean percent change from baseline of 32 percent on the modified CPRS-OC subscale, 33 percent on the Global O-C Scale, and 35 percent on the full CPRS-OC subscale. To answer the question of the influence of baseline depression on clomipramine response, the authors separated the group into more depressed or less depressed subgroups, using the mean Hamilton Depression Score of 12.2 as the dividing point. Judged by changes after 6 weeks of treatment in ratings of obsessions (*see* Table), the less depressed group appeared to show a superior response as shown in the Table, although this difference was not statistically significant. The depression changes were actually greater for the less depressed group, reflecting the greater magnitude of percent changes with a lower baseline.

To augment the group data, the authors used an intensive design for the study of a single case who became depressed in the course of the study. This patient's progress (*see* Figure), followed during two successive double-blind trials, of clomipramine, showed a similar change in obsessional ratings, although baseline Hamilton scores were 300 percent higher on the second trial.

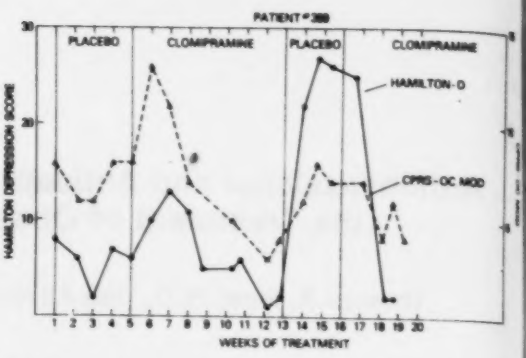

FIGURE. Progress for one subject on two successive double-blind trials of clomipramine.

While it does not appear that response to clomipramine requires or is even favored by high depression scores, is the antiobsessional response correlated with changes in mood? To answer this question the authors compared changes in the global ratings of obsessions and depression following 6 weeks of clomipramine treatment. The correlation for percent change from baseline for these two scales (completed simultaneously by the same rater) was nearly 0 ($r = -.03$), even though the means for percent change for these scales were nearly equal (34.9 ± 7.7 percent for depression, 32.6 ± 4.5 percent for obsessions).

Are the time courses for the two effects different? This question could not be answered comprehensively, as the authors had data at 2-week intervals in six subjects and weekly intervals in the remaining six. Still, the time of the peak change in global ratings of mood and obsessional symptoms could be compared in each subject. For six of the subjects, the peak change in mood was simultaneous with the improvement in obsessional symptoms. For five of the remaining six, the peak mood change preceded the peak change

Table

Baseline Scores and Percent Change on Clomipramine for More-Depressed and Less-Depressed Subgroups of Obsessive-Compulsive Patients

Groups		Baseline			Percent Change at 6 Weeks			
	N	Ham-D Range	Ham-D Mean	MOD CPRS-OC	CPRS-OC	MOD CPRS-OC	Global OC	Global Dep.
More Depressed	5	13-20	15.6	7.6	30.4	24.8	23.7	15.7
Less Depressed	7	7-11	9.7[a]	7.9	39.0	37.7	38.9	48.7[a]

[a] $p < .05$, two-tailed *t*-test for group means.

in obsessional symptoms by 2 to 4 weeks. In one subject, obsessional changes preceded the antidepressant effect. The overall mean for number of weeks to peak change was 3.8 for antidepressant effect and 4.7 for antiobsessional effect.

In summary, the evidence from this trial of clomipramine in OCD patients suggests:
1) Clomipramine's effectiveness for obsessional symptoms is independent of baseline depression ratings;
2) Changes in obsessional symptoms do not uniformly correlate with changes in mood, either in magnitude or time of occurrence;
3) Clomipramine's antiobsessional effects may occur slightly later than its antidepressant effects.

These results are surprising, in view of the accepted nosology that depressive symptoms in OCD are secondary. Indeed, in a separate study using a single dose of *d*-amphetamine, the authors showed a possible correlation between the changes in obsessional and depressive ratings (unpublished data). The lack of such a relationship with clomipramine may reflect the increasing number of confounding variables within a several weeks' trial as opposed to a few hours of treatment in the amphetamine study. Another possibility is that clomipramine, unlike *d*-amphetamine, works through two independent pharmacologic mechanisms to ameliorate a disorder of mood and a disorder of cognition and behavior.

Certainly the distinction between depressive and obsessional symptoms is not always clear. Exhaustion, self-reproach, and preoccupation with guilt are part of both affective and obsessional disorders. While these two disorders have been previously distinguished by different clinical courses (Welner et al. 1975), different rates of suicide (Goodwin et al. 1969), and different family incidences of affective illness (Coryell 1981), individual patients can have both OCD and severe depression. In general, if the depression begins subsequent to the obsessional complaints, it is considered a complication of OCD and, hence, a secondary depression. However, in some cases the depression seems to become autonomous, overtaking the obsessional symptoms.

Furthermore, the authors have reported a higher incidence of some of the psychobiologic manifestations of depressive disorders in OCD patients even without severe or even moderate affective symptoms. These variables include dexamethasone suppression tests (6 or 16 OCD patients escaped) and sleep electroencephalograph (EEG) records (OCD patients show reduced rapid-eye-movement latency and reduced Stage 4 sleep) (Insel et al. 1982). It may be that OCD biologically represents a variant of affective illness which is responsive to antidepressant treatment even in the absence of overt depression. Alternatively, these biological markers may be correlated with some phenomenon that the two syndromes have in common (e.g., anxiety or preoccupation with guilt). A third and not mutually exclusive hypothesis is that OCD is a chronic disorder that predisposes to affective illness, much as an immune deficiency state might predispose to infection. Perhaps the depression brings the patient to treatment, but because of the chronic obsessional disorder the usual affective manifestations are not evident, except as an exacerbation of ruminating or ritualizing. Thus, one would expect the biological manifestations of affective illness and response to antidepressant treatment independent of manifest depression.

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20th Annual Meeting of the ACNP—Poster Sessions

The following are papers based on poster sessions presented at the American College of Neuropsychopharmacology (ACNP) (December 1981) meeting. Abridged proceedings of papers presented a panels and workshops of the ACNP were included in Vol. 18, No. 3 of the *Psychopharmacology Bulleti*

Evaluation of Alpha-Adrenergic Responsiveness to Clonidine Challenge and Noradrenergic Metabolism in the Affective Disorders and Their Treatment

Larry J. Siever, M.D.,[1] Thomas W. Uhde, M.D.,[2] Edward K. Silberman, M.D.,[3] Charles R. Lake, M.D.,[4] David C. Jimerson, M.D.,[5] S. Craig Risch, M.D.,[6] Ned H. Kalin, M.D.,[1] and Dennis L. Murphy, M.D.[1]

Introduction

The dysregulation of noradrenergic activity hypothesized to be associated with the affective disorders and the alterations of activity accompanying antidepressant treatment may depend on the functional state of noradrenergic receptors. The physiologic and biochemical responses to the administration of clonidine, a selective α_2-adrenergic agonist, may permit an indirect evaluation of the responsiveness of these receptors. The growth hormone response to clonidin appears to be mediated by postsynapti α_2-adrenergic receptors in the hypothalamus and in animal studies, its magnitude may be cor related with α^2-adrenergic receptor sensitivity The hypotensive response may provide a mean of assessing the responsiveness of α_2-adrenergi autoreceptors. These and other responses t clonidine, as well as noradrenergic metabolites i controls and depressed patients before and during antidepressant treatment have been evaluated i an attempt to characterize noradrenergic recepto function in depression and its treatment.

[1]Clinical Neuropharmacology Branch, National Institute of Mental Health, Bethesda, MD 20205.
[2]Section on Psychobiology, Biologic Psychiatry Branch, National Institute of Mental Health, Bethesda, MD 20205.
[3]Laboratory of Psychology, National Institute of Mental Health, Bethesda, MD 20205.
[4]University of the Health Sciences Medical School, Department of Psychiatry and Pharmacology, Bethesda, MD 20814.
[5]Laboratory of Clinical Science, National Institute of Mental Health, Bethesda, MD 20205.
[6]Department of Psychiatry, School of Medicine, University of California at San Diego, La Jolla, CA 92093.

Methods

Clonidine was administered to 19 depressed pa tients (off all medications for 3 weeks) and 20 con trols (including 14 age- and sex-matched patient control pairs) and to 9 patients before and during the administration of clorgyline, a selective monoamine oxidase (MAO)-A inhibitor. Al women were tested within the 10 days following menses. Clonidine was administered intravenously over 5 minutes to subjects in the morning following an overnight fast, with plasma samples drawn at 15-minute intervals and blood pressure monitored at 5-minute intervals before and after clonidine administration. The averaged growth hormone response to clonidine during the first hour following clonidine administration was compared between the depressed patients and controls by the Mann-Whitney U Test. The averaged mean arterial pressure (MAP) between 45 and 60 minutes following the infusion was subtracted

from the averaged MAP in the 20 minutes prior to the infusion. The magnitude of the MAP decrement after chronic (greater than 21 days) treatment with clorgyline was compared by Student's *t*-test to the hypotensive decrease before treatment in the nine patients and to the hypotensive decrease after acute (2-3 days) and intermediate (10-14 days) treatment in three of these patients. Noradrenergic availability was indirectly assessed by determining plasma 3-methoxy-4-hydroxyphenylglycol (MHPG) and norepinephrine levels before and during the infusion, as well as urinary metabolite levels excreted over 24 hours prior to the clonidine study.

Table

Percent Fall of MAP Following Clonidine in Patients on Placebo and Long-term Clorgyline

Placebo	Clorgyline
11.7 ± 6.3 (S.D.)	2.4 ± 5.3 (S.D.)

Results

The growth hormone response to clonidine was significantly decreased in all ($p < .001$) subjects compared to controls as well as between age- and sex- matched depressed patients and controls ($p < .05$). This finding held up when subjects with elevated baseline growth hormone levels were either included or excluded. This response was negatively correlated ($r = -0.32, p < .05$, one-tailed test) with baseline plasma MHPG.

The hypotensive response to clonidine was significantly decreased after chronic clorgyline treatment ($p < .05$). No attenuation of the response was observed in the three patients tested after acute clorgyline treatment, with a slight apparent attenuation after intermediate duration treatment. The author's preliminary results do not suggest a consistent enhancement of the growth hormone response to clonidine after chronic clorgyline treatment.

Conclusions

The diminished growth hormone response to clonidine in depression is consistent with the results of other investigators (Checkley et al. 1981; Matussek et al. 1980) and raises the possibility that decreased postsynaptic α_2-adrenergic responsiveness may be associated with depression. Postsynaptic noradrenergic subsensitivity could conceivably contribute to a functional decrease in noradrenergic activity in depressed patients. The degree to which noradrenergic receptor responsiveness may be reciprocally related to presynaptic noradrenergic availability in depression deserves further exploration.

The attenuated hypotensive response to clonidine following chronic MAO inhibitor treatment is consistent with reports of a decreased hypotensive fall following chronic administration of the tricyclic desipramine (Charney et al. 1981; Checkley et al. 1981) and a previous report of patients on clorgyline and imipramine (Siever et al. 1981) and suggests that α_2-adrenergic autoreceptors may become subsensitive decreasing feedback inhibition of noradrenergic release, after chronic antidepressant treatment. The apparent lack of effect of acute treatment in our study suggests that this reflects a slow adaptive change rather than an acute effect such as α_2-adrenergic blockade. The time course of the decreased response to clonidine parallels that of the onset of clinical efficacy and of the decrease in blood pressure accompanying MAO inhibitor treatment, thus suggesting an important role for this adaptation in the MAO inhibitors and perhaps tricyclics' mechanism of action.

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Biological Markers for Depressive Illness

Alan G. Robertson, M.D.,[1] Betty Jo Tricou, M.D.,[1] Victor S. Fang, Ph.D.,[1,2] and Herbert Y. Meltzer, M.D.[1]

Introduction

Numerous investigators have reported a blunted thyroid stimulating hormone (TSH) response to thyrotropin-releasing hormone (TRH) in major depression (Extein et al. 1981; Gold et al. 1981; Kirstein et al. 1981).

There is evidence for the regulation of the hypothalamic-pituitary-thyroid axis by serotonergic neurons (Morley et al. 1981). Meltzer et al. (1981) reported a significant decrease in the number of serotonin (5-HT) uptake sites (V_{max}) in the blood platelets of unmedicated depressed patients.

This study investigated the TSH response to TRH and its relationship to ^{14}C-5-HT uptake in patients with major depressive illness, other psychiatric disorders, and controls.

Method

The subjects in these studies were newly admitted psychiatric patients and normal controls. Diagnoses were established according to Research Diagnostic Criteria (RDC).

The TRH test was carried out in 58 euthyroid patients and 19 euthyroid controls. All patients were drug-free for at least 7 days prior to testing and none had a history of lithium carbonate use within the preceding 6 months. After three baseline samples were obtained (-30′, -15′, 0′), 500 μg of TRH was infused at 10 a.m. over a 30-second period with subsequent blood samples taken at 15, 30, 60, 90, and 120 minutes. TSH was determined in duplicate by radioimmunoassay. Maximal TSH response (peak minus t_0 baseline) was determined for each subject. The TSH response to TRH was considered blunte for all subjects with ΔTSH ≤ 7 μU/ml and in separate statistical analysis for all subjects wit ΔTSH < 5.0μU/ml.

The method of 5-HT uptake determination ha been previously reported (Arora & Meltzer 1981). V_{max} and K_m were determined on two occasion in patients who had been drug-free for at leas 7 days. Results were averaged.

Table 1

Comparison of Mean ΔTSH Following TRH in Unipolar Depression, Other Diagnostic Groups, and Controls

Diagnosis	N	ΔTSH[a]	t
Males and Females			
Unipolar depression	12	6.8 ± 4.2	—
Bipolar depression	6	11.8 ± 4.7	2.28[b]
Schizoaffective depression	13	13.5 ± 9.7	2.20[b]
Bipolar, minor, and schizoaffective depression	23	12.8 ± 7.9	2.43[b]
All diagnoses other than unipolar depression	46	12.0 ± 7.3	2.63[b]
Controls	13	11.6 ± 7.2	2.00[c]
Males			
Unipolar depression	8	4.6 ± 2.8	—
Bipolar, minor, and schizoaffective depression	9	8.8 ± 4.8	2.22[b]
All diagnoses other than unipolar depression	22	10.6 ± 5.6	2.80[b]
Controls	8	10.8 ± 7.2	2.24[b]

[a] μU/ml (Mean ± S.D.)
[b] Compared to unipolar depression, $p < .05$.
[c] Compared to unipolar depression, $p < .10$.

Results

Of 19 nonpatient controls given TRH, 500 μg, i.v., six had a personal history of previous minor depression, excess alcohol use, or a family history of treated depressive disorders. Five of these six controls had a blunted TSH response (ΔTSH < 5 μU/ml), whereas none of the other 13 did.

The proportion of patients and controls with a blunted TSH response varied greatly depending upon which criterion (ΔTSH < 5 or ΔTSH ≤ 7 μU/ml) was used because the response of many subjects fell within the 5-7 μU/ml range. Eight of 12 (66.7%) unipolar depressed patients had a

[1] Department of Psychiatry, University of Chicago Pritzker School of Medicine and the Illinois State Psychiatric Institute, Chicago, IL 60612.
[2] Department of Medicine, University of Chicago Pritzker School of Medicine, and the Illinois State Psychiatric Institute, Chicago, IL 60612.

significantly ($p < .05$) greater proportion of blunted responses (ΔTSH ≤ 7 μU/ml) than the combined group of bipolar, minor, and schizoaffective depressed patients (6/23, 26.1%). Fifteen of 46 (32.6%) patients with other psychiatric disorders (schizophrenia, mania, schizoaffective mania, unspecified functional psychosis, personality disorder, generalized anxiety disorder, obsessive compulsive disorder, anorexia nervosa, and drug use disorder) also had a blunted TSH response. The sensitivity of the TRH test for unipolar depression (primary and secondary) was 66.7 percent and the specificity 67.4 percent, using ΔTSH ≤ 7 μU/ml as the criterion.

The unipolar depressives had a significantly lower mean ΔTSH response than the 1) bipolar depressives, 2) schizoaffective depressives, 3) bipolar, minor, and schizoaffective depressives, and 4) patients with diagnoses other than unipolar depression (Table 1). Male unipolar depressives had a significantly lower mean ΔTSH response than male controls (Table 1). Secondary major depressives ($N=5$) had a significantly ($p < .05$) lower mean ΔTSH response than patients with primary major depression ($N=7$). There was no significant correlation between the severity of depression as measured by Hamilton scores and the ΔTSH response to TRH.

Peak TSH levels after TRH infusion were reassayed in duplicate by the thyroid laboratory of the University of Chicago Medical Center in 22 patients and controls. Although there was good correlation between both assays ($r=0.953$), the absolute levels differed by 1.5-2 μU/ml in the critical 5-7 μU/ml range.

Results of the TSH response to TRH and platelet 5-HT uptake were available for 20 patients with major depression or schizoaffective depression, mainly affective type (Table 2). V_{max} of 5-HT uptake was significantly decreased in patients with a ΔTSH response of ≤ 7 μU/ml compared to normal controls. K_m of 5-HT uptake was significantly lower in patients with a ΔTSH response of ≤ 7 μU/ml compared to patients with a ΔTSH response of >7 μU/ml and to normal controls.

Table 2

Relationship of TSH Response to TRH and ^{14}C-5-HT Uptake in Major Depressed and Schizoaffective Depressed, Mainly Affected Patients

	N	Mean ± S.D. K_m[a]	Mean ± S.D. V_{max}[b]
Patients	20	0.43 ± 0.16[e]	10.94 ± 3.10[c]
ΔTSH ≤ 7 μU/ml	11	0.37 ± 0.12[d,e]	10.16 ± 2.60[c]
ΔTSH >7 μU/ml	9	0.52 ± 0.16	11.86 ± 3.54
Controls	55	0.51 ± 0.14	12.74 ± 3.08

[a] K_m indicates the apparent Michaelis constant; the values are micromolar.
[b] V_{max} indicates maximum velocity; the values are picomoles per 10^7 platelets per minute.
[c] $p < .05$ compared to controls.
[d] $p < .05$ compared to patient group ΔTSH > 7 μU/ml.
[e] $p < .005$ compared to controls.

Discussion

The sensitivity (66.7%) of a blunted TSH response to TRH to identify unipolar depression using a criterion of ΔTSH ≤ 7 μU/ml was in the range as previously reported by Extein et al. (1981), Gold et al. (1981), and Kirstein et al. (1981) who found the TSH response to TRH was useful in confirming the diagnosis of major unipolar depression. The finding of a lower specificity (67.4%) may be due to differences in studies in the diagnostic compositions of patient groups with diagnoses other than unipolar depression.

The finding of a significantly lower mean ΔTSH response in unipolar depression compared to bipolar depression has been previously reported by Gold et al. (1980), but was not confirmed by Bjørum and Kirkegaard (1979). The finding of a significantly lower mean ΔTSH response in secondary major depression compared to primary major depression is opposite to the results reported by Gold et al. (1980).

Finding blunted TSH responses in five of six volunteers with previous minor depression, excess alcohol use, or family history of treated depression indicates the need for careful evaluation of control subjects and their families. This study also indicates the need for an extremely reliable and reproducible means of TSH determination and for each laboratory to determine the limit of the normal TSH response to TRH.

Decreased V_{max} of platelet 5-HT uptake appears to have great promise as a marker of

vulnerability to major depressive illness (Meltzer et al. 1981). The association between a blunted TSH response to TRH and decreased V_{max} and K_m values provides some clue to the nature of a blunted TSH response which may be related to an abnormality of the serotonergic system.

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Relationship of Dexamethasone (2 mg) and Plasma Cortisol Hypersecretion in Depressive Illness: Clinical and Neuroendocrine Parameters

Gregory M. Asnis, M.D.,[1] Uriel Halbreich, M.D.,[2] Edward J. Sachar, M.D.,[1] R. Swami Nathan, M.D.,[3] Mark Davies, M.P.H.,[1] Hana Novacenko, M.S.,[1] Lynn C. Ostrow, R.N., M.A.,[1] Jean Endicott, Ph.D.,[1] and Joaquim Puig-Antich, M.D.[1]

Dexamethasone (2 mg) resistance and cortisol hypersecretion are two neuroendocrine abnormalities seen in approximately 1/3 to 1/2 of endogenously depressed patients (Brown et al. 1979; Carroll et al. 1976a, 1976b; Sachar et al. 1970; Stokes et al. 1975). Both neuroendocrine disturbances are presumed to reflect increased hypothalamic-pituitary-adrenal activity. The investigators studied the above neuroendocrine assessments in the same group of endogenously depressed patients. The focus was upon the relationship of various clinical correlates with dexamethasone resistance and plasma cortisol hypersecretion; the main hypthesis was that if both tests of cortisol abnormality were associated with specific depressive symptoms, then they were more likely to reflect similar underlying mechanisms.

Method

Thirty depressed patients (10 men and 20 women, mean age ± SD = 44.2 ± 14.4 years, range = 18-64 years) were admitted to an inpatient research ward where they were evaluated with the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott & Spitzer 1978) and were diagnosed according to the Research Diagnostic Criteria (RDC) (Spitzer et al. 1978) as

[1]New York State Psychiatric Institute and College of Physicians and Surgeons of Columbia University, New York, NY 10032.
[2]Present Address: Montefiore Hospital and Medical Center, Bronx, NY 10467.
[3]Western Psychiatric Institute and Clinic, Pittsburgh, PA 15261.

having a major depressive disorder, endogenous subtype; patients had to have at least a moderately severe depression (Hamilton ≥ 18) (Endicott, et al. 1981). All subjects were free of psychotropic medication for a minimum of 10 days prior to being studied, were medically healthy, and were not taking any hormone pills.

Demographic data, RDC depressive subtypes, SADS-C scales (symptom clusters relating to the past week), and a scale constructed by the authors of "Hypothalamic Signs" (insomnia, poor appetite, psychomotor retardation, worsening of mood in the morning) were systematically obtained on all subjects.

All subjects received the 2 mg dexamethasone suppression test (DST)* and a mean 1 to 4 p.m. plasma cortisol assessment. Two mg of dexamethasone were taken orally at 11 p.m. with postdexamethasone plasma cortisol assessed at 4 and 11 p.m. the following day. Resistance to dexamethasone was defined as a postdexamethasone plasma cortisol value of >5 μg/dl. Plasma cortisol was analyzed by a modified competitive protein binding method as described by Novacenko et al. (1980). Subjects received a basal plasma cortisol assessment prior to the DST. An angiocatheter was inserted in the antecubital vein at 9 a.m. with blood sampling (3 cc) every 30 minutes for 24 hours; 26 or the 30 subjects had a complete study while 4 subjects had their study terminated prematurely (but after 4 p.m.) due to subcutaneous infiltration of the angiocatheter. Thus, all subjects had a 1 to 4 p.m. study, and the mean plasma cortisol for this period was used as an integrated measure of plasma cortisol secretion. This was done because the mean 1 to 4 p.m. plasma cortisol has been shown to highly correlate with the mean 24-hour cortisol in normals and depressives (Halbreich et al. 1981, 1982). In the 26 subjects who had a complete 24-hour study, the mean 1 to 4 p.m. plasma cortisol was also highly correlated to the mean 24-hour plasma cortisol, $r = 90$, $p < 0.001$.

A more extensive evaluation of the mean 1 to 4 p.m. plasma cortisol was undertaken in 32 normal volunteers and 52 endogenously depressed patients in order to determine a satisfactory cortisol level to define cortisol hypersecretion (*see* Figure 1). A mean 1 to 4 p.m. plasma cortisol of >10 μg/dl was used to define cortisol hypersecretion. This criterion was met in 2 of 32 normals (6 percent) and 20 of 52 (40 percent) depressives (Fisher Exact Probability Test, $p = 0.027$).

Results

Eight of 30 (27%) patients were dexamethasoneresistant and 12 of 30 (40%) patients were defined as cortisol hypersecretors.

Age

Patients with dexamethasone resistance were not significantly different in age from suppressors (45.0 SD 14.2 years vs. 42.2 SD 15.8 years, $F = 0.02$, NS); however, cortisol hypersecretors were significantly older than cortisol normosecretors (51.7 SD 12.7 years vs. 39.3 SD 13.7 years, $F = 6.25$, $p < .02$). A positive relationship between age and cortisol hypersecretion in endogenous depressives had been reported previously by Asnis et al. (1981). Subsequent analyses reported below controlled for age.

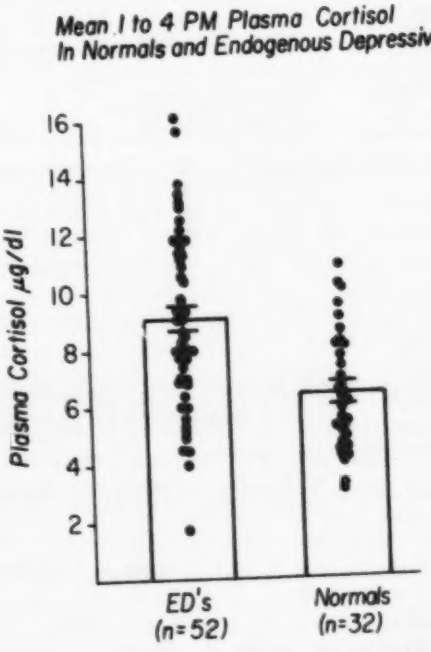

FIGURE 1. Mean 1 to 4 p.m. plasma cortisol in normals and endogenous depessions (EDs).

*There are two versions of the DST: one uses 1 mg, the other uses 2 mg.

Sex

Two of 10(20%) men vs. 6 of 20(30%) women were dexamethasone resistant (Fisher exact test, NS); 4 of 10 (40%) men vs. 8 of 20 (27%) women were cortisol hypersecretors (Fisher exact test, NS).

SADS-C Scales

As can be seen in Table 1, the patients with dexamethasone resistance had significantly higher scores on the scale "Hypothalamic Signs"; the symptom of this scale which was significantly associated with dexamethasone resistance was

Table 1

The Relationship of SADS-C and Summary Scales to Dexamethasone Resistance and Cortisol Hypersecretion in Endogenously Depressed Patients

	Depressive Syndrome	Endogenous Features	Manic Syndrome	Anxiety	Delusions-Hallucinations Disorganization	GAS Score
Dexamethasone Resistance ($N = 8$ vs. 22)	4.01	3.90	2.76	0.09	0.01	0.08
Cortisol Hypersecretion ($N = 12$ vs. 18)	0.47	0.02	2.86	1.26	0.69	0.12

	Extracted Hamilton	Miscellaneous Psychopathology	Social Functioning	Suicidal Behavior	Hypothalamic[a] Signs
Dexamethasone Resistance ($N = 8$ vs. 22)	0.66	2.49	0.92	0.09	7.20[b]
Cortisol Hypersecretion ($N = 12$ vs. 18)	0.03	4.51[c]	0.98	0.01	0.03

[a] Hypothalamic signs consist of a cluster of symptoms from endogenous feature scale (insomnia, poor appetite, psychomotor retardation, worse in morning) felt to be specific for hypothalamic dysfunction.

[b] $p < .01$

[c] $p < .05$

Table 2

The Relationship of RDC Depressive Subtypes to Dexamethasone Resistance and Cortisol Hypersecretion in Endogenously Depressed Patients

	Psychotic	Bipolar	Retarded	Agitated	Simple	Situational	Primary	Incapacitated
Dexamethasone Resistance ($N = 8$ vs. 22)	0.175	0.056	[a]0.018	0.574	0.637	0.426	0.548	0.282
Cortisol Hypersecretion ($N = 12$ vs. 18)	0.455	0.350	0.132	0.251	0.197	0.206	0.350	0.588

[a] Statistically significant

psychomotor retardation ($F = 10.12$, $p < .004$). In contrast, patients with cortisol hypersecretion had significantly higher scores on the scale Miscellaneous Psychopathology (the significant symptom in this scale was subjective anger) ($F = 10.83$, $p < .003$).

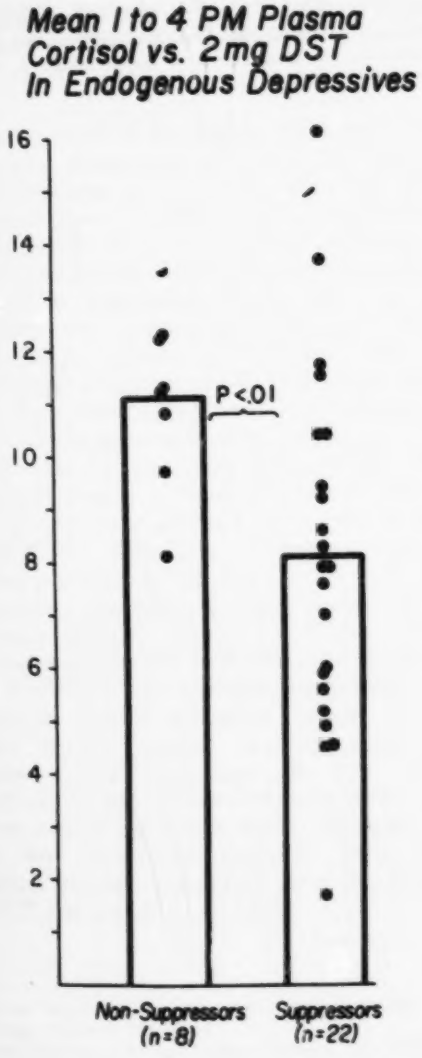

FIGURE 2. Mean 1 to 4 p.m. plasma cortisol vs. 2 mg DST in endogenous depressives.

RDC Subtypes

As can be seen in Table 2, dexamethasone resistance was significantly associated with retarded depression (trend for bipolar depression) while cortisol hypersecretion was not significantly associated with any depressive subtype.

The Association of the 2 Mg DST and Mean 1 to 4 P.M. Plasma Cortisol

As can be seen in Figure 2, nonsuppressors had a significantly higher mean 1 to 4 p.m. plasma cortisol (11.1 ± 1.6 μg/dl) than the suppressors (8.1 ± 3.4 μg/dl) ($F = 8.24$, $p < .01$). Six of 8 nonsuppressors were cortisol hypersecretors in comparison to 6 of 22 suppressors (Fisher exact test, $p = .027$). Although there is an association of the 2 mg DST and plasma cortisol hypersecretion, only 50 percent of the cortisol hypersecretors (6 of 12 patients) were identified by the 2 mg DST. On the other hand, two dexamethasone nonsuppressors were normosecreters.

Within the 12 cortisol hypersecretors, mean 1-4 p.m. cortisol did not predict DST−2 mg. nonsuppression ($r = -.14$, NS).

Discussion

The phenomenon of dexamethasone resistance (2 mg DST) and plasma cortisol hypersecretion were studied in the same 30 endogenously depressed patients. The clinical correlates associated with dexamethasone resistance were RDC subtype (retarded depression) and the summary scale of "Hypothalamic Signs" (the significant symptom being psychomotor retardation). These correlates were different from those associated with plasma cortisol hypersecretion, i.e., older age and the summary scale of Miscellaneous Psychopathology (the significant symptom was subjective anger). These clinical correlates need replication and may reflect the particular sample studied. Thus, a larger sample size may be necessary to firm up these findings.

In addition with two exceptions, DST−2 mg basically identified a subset of cortisol hypersecretors, although the mean 1-4 p.m. plasma cortisol within the group of hypersecretors did not predict DST−2 mg resistance. Dexamethasone

(2 mg) does not simply inhibit "milder" cortisol hypersecretors. Even some normosecretors may escape the suppressant effect of DST−2 mg.

The implication of these clinical/neuroendocrine findings is that the complexity of dysregulation of cortisol secretion in major depressives is not fully understood. Interestingly, both measures of cortisol secretion are associated with depressive illness, but the data reported here do not in any way fit a linear univariate model nor do they identify underlying mechanisms for DST− 2 mg and cortisol hypersecretion.

Several measures (DST−1 mg, *d*-amphetamine test) of cortisol secretion in the same sample of depressives and both normal and pathological controls should illuminate further the pathophysiology of depressive illness and the diagnostic utility of one (or several) tests of cortisol secretion.

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Melatonin Secretion as a Neurobiological "Marker" and Effects of Light in Humans

Alfred J. Lewy, M.D.,[1] Thomas A. Wehr, M.D.,[2] Norman E. Rosenthal, M.D.,[2] John I. Nurnberger, M.D.,[2] Larry J. Siever, M.D.,[2] Thomas W. Uhde, M.D.,[2] David A. Newsome, M.D.[3] Leslie E. Becker, M.D.,[2] Sanford P. Markey, Ph.D.,[2] Irwin J. Kopin, M.D.,[2] and Frederick K. Goodwin, M.D.[2]

Development of the highly accurate and sensitive gas chromatographic-negative chemical ionization mass spectrometric assay for plasma melatonin (Lewy & Markey 1978) has facilitated evaluation of pineal function in humans. The pineal gland synthesizes and secretes melatonin in response to stimulation of its beta-adrenergic receptors by norepinephrine released by postganglionic sympathetic neurons, the nervi conarii (Ariëns Kappers 1960; Deguchi & Axelrod 1972). Beta-adrenergic stimulation initiates a sequence of biochemical events, culminating in increased activity of N-acetyltransferase, which converts serotonin to N-acetylserotonin, the rate-limiting step in melatonin synthesis (Klein & Weller 1970). The firing of these sympathetic neurons is discretely regulated by an endogenous pacemaker, thought to be located in the suprachiasmatic nucleus (SCN) of the hypothalamus (Moore & Eichler 1972; Stephan & Zucker 1972). The endogenous pacemaker is responsible for a circadian (about 24-hour) rhythm in the activity of these sympathetic neurons. The circadian rhythm in the hypothalamic pacemaker is synchronized to the environmental light/dark cycle, through input from the retinohypothalamic tract which transmits photic information from the retina to the SCN (Moore & Lenn 1972).

[1]Sleep and Mood Disorders Laboratory, Oregon Health Sciences University, Portland, OR 97201.
[2]National Institute of Mental Health, Bethesda, MD 20205.
[3]National Eye Institute, Bethesda, MD 20205.

Send reprint requests to: Dr. A.J. Lewy, Department of Psychiatry, Oregon Health Sciences University, Portland, OR 97201.

There are essentially two effects of light on the circadian system, one, the light/dark cycle entrains (synchronizes) circadian rhythms (Aschoff 1981) and two, the changing length of darkness throughout the year cues seasonal rhythms (Pittendrigh 1981). An additional unique effect of light (specific to the pineal) is that acute exposure to light suppresses melatonin production (Minneman et al. 1974). It is assumed that all three effects of light are mediated by the same neural pathways. Consequently, measurement of light suppression of melatonin may be a "marker" for the effects of light on the circadian system.

The human pineal appears to be regulated in the same way as is the pineal of other mammalian species, because nighttime secretion of melatonin is suppressed by bright artificial light and sunlight in humans (Lewy et al. 1980). Light also appears to be important for the proper synchronization of the circadian rhythm of melatonin secretion, because some blind people have unusual circadian secretory rhythms (Lewy & Newsome 1982).

Manic-depressive patients seem to be supersensitive to light (Lewy et al. 1981). Four patients (taking no medications in seven out of eight instances) were studied in both mood states. Exposure to 500 lux Vita-Lite suppressed the patients by 50 percent; this intensity had little or no effect in a normal control group ($N = 6$). This difference was statistically significantly different ($p < .02$, by analysis of variance). An additional group of five euthymic manic-depressive patients were also studied. Melatonin secretion was suppressed by 50 percent with 500 lux light in this group as well. Thus, supersensitivity to light may be a "trait marker" for manic-depressive illness. Supersensitivity to light is consistent with, and could possibly explain, phase-advanced circadian rhythms observed in these patients (Wehr & Goodwin 1981). More subjects, including a group of unipolar patients, are currently being studied. Also, preliminary evidence suggests that there may be a seasonal rhythm in light sensitivity in both patients and normal controls, because subjects appear to suppress more during the winter than during the summer.

Light supression of melatonin secretion has some potentially important implications—the circadian rhythms of humans may be synchronized by the light/dark cycle and humans may have seasonal rhythms that are affected by the chang-

ing length of daylight Ordinary artificial light apparently does not affect human melatonin secretion (Lewy et al. 1980), implying that human circadian and seasonal rhythms may not be perturbed by indoor lighting under usual circumstances. Consequently, humans may be similar to other species in that they may be affected by the 24-hour rhythm of sunlight and by the length of natural daylight as it changes throughout the year (Aschoff 1981).

Photoperiodic effects of light were evaluated in humans by exposing a man with winter depression to "long days" of light during the winter of 1980 (Lewy et al. 1982a). A manic-depressive patient with a well-documented 13-year history of winter depressions and springtime remissions was exposed to 2000 lux Vita-Lite between 6 and 9 a.m. and between 4 and 7 p.m. for 10 days. Within 4 days his winter depression remitted. Although this is an $N = 1$ study, it is the first attempt to use light to treat a manic-depressive patient with a disorder that appears to be related to the circadian system. More patients were studied during the winter of 1981 using a modified crossover design with dim light as a placebo control. (Ordinary dim room light would not be expected to directly affect the circadian system of humans.) Bright light combined with sleep deprivation as a treatment for depression is also being evaluated.

Melatonin levels are also a marker for adrenergic function. Human melatonin secretion appears to be regulated by beta-adrenergic receptors. Transection of the spinal cord abolishes the circadian melatonin secretory rhythm (Kneisley et al. 1978). Sympatholytic diseases, such as Shy Drager Syndrome and idiopathic orthostatic hypotension, result in either reduced plasma melatonin and urinary 6-hydroxymelatonin levels or disrupted secretory rhythms Tetsuo et al. 1981; Vaughan et al. 1979). Administration of propranolol reduces the nighttime rise in melatonin levels (Hanssen 1977; Vaughan 1976). Bedtime administration of 120 mg daily (p.o.), can completely reduce nighttime melatonin levels (authors' unpublished data).

Clonidine can also reduce nighttime levels (Lewy et al. 1982b). Clonidine was administered intraventricularly (i.v.) to four normal volunteers around midnight at doses of 2.0, 2.5, and 3.0 µg/kg. There was a linear log dose reduction of plasma melatonin levels 1 hour after administration of clonidine compared to the same time on a baseline night ($r = -.986$, $p < .01$). Oral administration of clonidine is also effective; administration by this route has a delayed onset of action and a longer duration of action than after i.v. administration. Measurement of urinary 6-hydroxymelatonin may also be a useful way of quantifying the effects of clonidine on melatonin production. Presumably, clonidine acts on an alpha-adrenergic receptor, although the exact location of this receptor has yet to be identified. [The only alpha-receptor localized so far in the retino-hypothalamic-pineal system has been a presynaptic alpha-2-autoadrenoceptor on the sympathetic neuron innervating the pineal (Pelayo et al. 1977).]

Summary

Plasma melatonin levels are a marker for adrenergic function; the rhythm of melatonin production is a marker for the phase and period of its endogenous pacemaker; suppression of melatonin secretion by light is a marker for the effects of light in humans. Bright light appears to have similar biological effects in humans as does ordinary room light in other species. Light suppression of melatonin may prove to be a valuable research tool; light may also have potential as a therapeutic modality for certain circadian and seasonal disorders.

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The Relationship of Plasma-Free MHPG to Anxiety and Psychophysical Pain in Normal Volunteers

Thomas W. Uhde, M.D.,[1] Larry J. Siever, M.D.,[2] Robert M. Post, M.D.,[1] David C. Jimerson, M.D.,[3] Jean-Philippe Boulenger, M.D.,[1] and Monte S. Buchsbaum, M.D.[1]

Alterations in noradrenergic function have been postulated in theories of anxiety and pain. In animals, lesions of the noradrenergic nucleus locus coeruleus produce decreased fear-associated behaviors (Redmond & Huang 1979) and analgesia (Bodnar et al. 1978). Pharmacologic inhibition of the locus coeruleus also produces effects in a similar direction. That is, morphine (Korf et al. 1974) and clonidine (Aghajanian 1978) inhibit locus coeruleus activity, reduce fear-associated behaviors (Redmond 1977; Redmond & Huang 1979), and have potent analgesic (Fielding et al. 1981; Paalzow 1974) properties. Tricyclic antidepressants decrease locus coeruleus firing (Redmond 1977; Redmond & Huang 1979), produce analgesia in some animals, and potentiate morphine-induced antinociception (Malseed & Goldstein 1979). Although electrical and pharmacologic (Redmond 1977; Redmond & Huang 1979) activation of the locus coeruleus is associated with increased fear-associated behaviors, the effect of increased noradrenergic function on antinociception remains uncertain (Pert 1980). These observations may suggest a linkage between the biological functions of anxiety and pain. It is interesting in this regard that morphine is generally accepted to have analgesic and antianxiety properties in man. Furthermore, tricyclic antidepressants are effective in the treatment of patients with panic disorder (Klein 1964)

[1]Biological Psychiatry Branch, National Institute of Mental Health, Bethesda, MD 20205.

[2]Clinical Neuropharmacology Branch, National Institute of Mental Health, Bethesda, MD 20205.

[3]Laboratory of Clinical Science, National Institute of Mental Health, Bethesda, MD 20205.

Address reprint requests to: Uhde, M.D., Biological Psychiatry Branch, Building 10, Room 3S-239, National Institute of Mental Health, 9000 Rockville Pike, Bethesda, MD 20205.

and certain pain syndromes (Merskey & Hestes 1972). Clonidine also has antianxiety effects in depressed (Uhde et al. 1981) and anxious patients (Hoehn-Saric et al. 1981; Liebowitz et al. 1981; Uhde et al. 1982), but not normal volunteers (Leckman et al. 1980; Uhde et al. 1981, 1982). Although clonidine at low doses does not produce analgesic effects in human controls as a group (Uhde et al. 1980, 1982), both clonidine and morphine produce predictable changes in a subgroup of insensitive subjects in the direction of increased analgesia as reflected by somatosensory evoked potentials (Buchsbaum et al. 1982). Benzodiazepines, which decrease locus coeruleus firing (Grant et al. 1980), recently have been reported to influence endogenous opioid systems (Duka et al. 1979; Soubrie et al. 1980).

Together, these data may suggest a functional relationship between the noradrenergic system and the experience of anxiety and pain. In attempts to collect data pertinent to these variables the authors have investigated the relationship among plasma free 3-methoxy-4-hydroxyphenylethylene glycol (MHPG), state anxiety, and psychophysical pain in 12 normal volunteers.

Method

Psychophysical Pain

Using previously described methods (Davis et al. 1978), an index of pain insensitivity was obtained in 12 normal volunteers 1-1½ hours after the blind administration of a placebo infusion which had been randomly paired with an active medication. Subjects received shocks at each milliamperage (mA) increment from 1 to 31, for a total of 93 randomly presented shocks. Subjects judged each shock as noticeable, distinct, unpleasant, or very unpleasant. An index of pain insensitivity was obtained by threshold and signal detection analysis. This index is derived from the subject's ability to distinguish between distinct and unpleasant sensations. Increases in this measure have been associated with morphine and aspirin analgesia (Buchsbaum & Davis 1979; Davis et al. 1980), and decreases with naltrexone-induced hyperalgesia in schizophrenics (Davis et al. 1979).

State Anxiety

The Spielberger State Trait Anxiety Inven (range 20-80) was administered 1-1½ hours a the placebo infusion (just prior to the admini tion of the shocks).

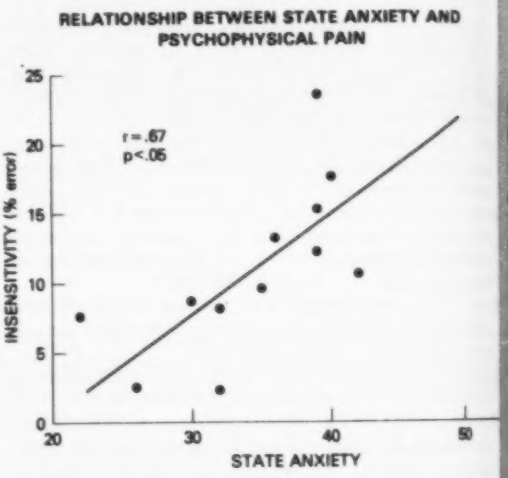

FIGURE 1. Those normal volunteers with higher rati of state anxiety demonstrated increased pain insensitiv as measured by threshold and signal detection analys

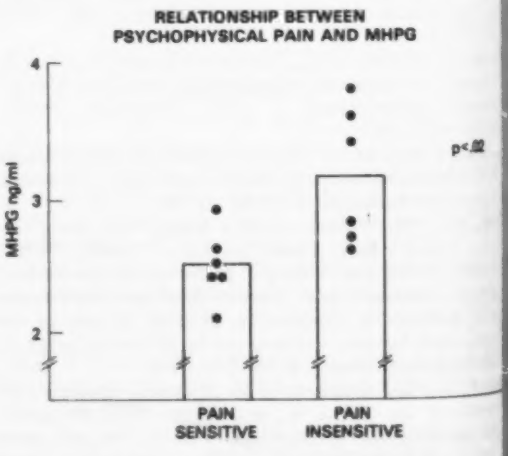

FIGURE 2. In the first 12 normal subjects studied, the most pain-sensitive subjects had lower values of plas free MHPG than the six most pain-insensitive subjec

iological Measures

Plasma-free MHPG was measured by gas hromatography-mass spectrometry (Jimerson et l. 1981). All results refer to data obtained after he placebo infusion and, therefore, just prior to he administration of shocks.

Results

There were significant correlations between tate anxiety and scores on the insensitivity index = .67, $N = 12$, $p < .05$) (Figure 1) and state nxiety and plasma-free MHPG ($r = .59$, $N = 12$, $< .05$). Thus, the subjects with the highest atings of state anxiety had the greatest plasma-ree MHPG and were least able to discriminate etween distinct and unpleasant sensations. By nedian split, the six most pain insensitive in-ividuals had significantly higher levels of lasma-free MHPG (3.2 ng/ml ± 0.2 S.E.) Figure 2) and anxiety (39.1 ± 1.8) compared to he six least pain insensitive individuals (MHPG .5 ± 0.1, $p < .02$; anxiety 27.8 ± 1.6, $p <$ .001).

Discussion

Our data suggest that the greater the state anx-ety, the greater the insensitivity and inability to discriminate among randomly administered hocks. Individuals with low MHPG were less nxious and more pain sensitive than those sub-ects with relatively higher MHPG. These find-ngs support previous observations of a relation-hip between anxiety and noradrenergic function nd suggest that high anxiety in normal controls nay reduce the ability to discriminate the amount f pain an individual feels. This rather unique elationship in normals is opposite the usual ex-pectation of clinicians treating patients with hronic pain. That is, pathological anxiety in hronic pain patients is often thought to decrease ain thresholds. Preliminary evidence from the uthors' laboratory also suggest that patients with hronic pathological anxiety may become more ain sensitive with increasing degrees of state nxiety. Increases in state anxiety, therefore, may ave opposite effects on pain discriminability in normal controls compared to patients with chronic anxiety disorders, suggesting that the relationship between anxiety and pain may be nonlinear.

The authors' findings suggest that reducing some patients' anxiety with anxiolytics might intensify, rather than decrease, the amount of pain experienced as measured by the insensitivity index. If this hypothesis is correct it might explain why clonidine, which has acute antianxiety effects in depressed and phobic anxious patients, lacked group analgesic activity in normal human volunteers as measured by the insensitivity index (Uhde et al. 1980, 1981, 1982). These findings in man support and extend previous animal research suggesting an important role for noradrenergic systems in the modulation of anxiety and pain.

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Current Knowledge of Tricyclic Antidepressant Response Indicators

David H. Tilley, M.P.H.,[1] Solomon C. Goldberg, Ph.D.,[1] and Robert O. Friedel, M.D.[1]

Since the early 1960s, a substantial amount o clinical research has been aimed at refining an targeting the therapeutic application of tricycli antidepressants (TCA). Attempts to detect mean ingful correlations between patient characteristic and treatment response have been an importa aspect of this work. Symptoms, patient histor personality variables, and biological markers hav been and are currently being studied for the response indicator value.

In order to characterize the current state o knowledge of TCA response indicators, th authors have reviewed the literature (controlle clinical research and nodal review articles) an polled substantial panels for expert and practi tioner opinion among psychiatrists. The exper panel consisted of productive and widely accepte researchers in the field drawn from the Americ College of Neuropsychopharmacology (ACNP membership roster and literature citation. Th practitioner panel consisted of members of th Virginia Neuropsychiatric Society who "frequen ly" use TCA in the treatment of depressed pa tients. Panel respondents were presented with list of 41 proposed response indicators and aske to classify each item as 1) indicative of positive clinical response to TCA, 2) indicative of non response (no better than placebo), or 3) of no in dicative value with respect to TCA response.

The authors consider both homogeneity an diversity among sources helpful in understandin their current state of knowledge, in identifyin areas which merit further research attention, an in forming research questions and hypotheses The following tables display the more interestin areas of agreement and disagreement amon sources, and provide some insight with respect t currently important questions:

[1]Medical College of Virginia, Richmond, VA 23298.

1. Does the expert panel agree on anything or is there no consensus on the state-of-the-art regarding TCA response indicators?
2. To what extent do general psychiatric practitioners agree or disagree with expert opinion?
3. How does accumulated clinical wisdom compare with findings reported in the literature?

Areas of Agreement

Agreement among panel members and between panels is so strong with respect to the first 10 indicators shown in Table 1, that they might reasonably be considered current clinical knowledge. The virtual coincidence of these items and Diagnostic and Statistical Manual-III (DSM-III) criteria for melancholia supports the proposition that TCA therapy is an appropriate treatment for the disorder.

Table 1

Positive Response Indicators on Which Experts and Practitioners Agree

Indicator	Expert Panel (% +)	Practitioner Panel (% +)
Weight loss	82	9[illegible]
Early morning awakening	79	9[illegible]
Psychomotor retardation	89	94
Loss of appetite	82	94
Primary depression	86	93
Prior episodes	82	90
Poor concentration	68	88
Anhedonia	75	68
Better in evening	68	78
Blames self	68	83
Midnight awakening	64	76
Fatigue and lethargy	61	75

Table 2

Nonresponse Indicators on Which Experts and Practitioners Agree

Indicator	Expert Panel (% −)	Practitioner Panel (% −)
Inadequate personality	71	83
Secondary to antisocial personality	72	86
Hallucinations	75	83
Energetic	64	86
Delusions	75	63

While Table 2 (nonresponse indicators) shows substantial agreement on three items (inadequate personality, secondary to antisocial personality disorder, and hallucinations), no nonresponse indicator achieved the level of concurrence demonstrated for the six leading positive indicators (Table 1). Both panels responded with more agreement to positive indicators than to nonresponse indicators. In addition to the items shown in Table 2, there was fair concurrence on the nonresponse indicative value of other items describing "secondary depression" (secondary to alcoholism, secondary to schizophrenia, and secondary to obsessive-compulsive disorder).

Table 3 compares panel results with results cited in literature reviews. The positive indicative value of vegetative signs of depression (weight loss, early morning awakening, and psychomotor retardation) is strongly and consistently supported by the literature. Anhedonia, anorexia, and self-reproach are supported by panel responses as indicators of positive TCA response, but the literature is less conclusive. The literature is of little help in verifying the indicative value of primary depression, prior episodes, poor concentration, and diurnal variation. *None of the nonresponse indicators selected by the authors' panels showed consistent results in the literature.*

Table 3

Concensus Indicators Compared to the Literature

Indicator	Bielski and Friedel[a]	Nelson and Charney[b]
Weight loss +	+	slight +
Early morning awakening +	+	slight +
Psychomotor retardation +	+	strong +
Primary depression +	-----	-----
Prior episodes +	-	-----
Poor concentration +	-----	-----
Anhedonia +	-----	moderate +
Better in evening +	-----	-----
Loss of appetite +	+	-----
Blames self +	-----	moderate +
Inadequate personality -	-----	-----
Secondary to antisocial personality -	-----	-----
Energetic -	-----	-----
Hallucinations -	-----	-----

[a] Bielski, R.J., and Friedel, R.O. Prediction of tricyclic antidepresant response: A critical review. *Arch. Gen. Psychiatry*, 33:1487-1499, 1976.

[b] Nelson, J.C., and Charney, D.S. The symptoms of major depressive illness. *Am. J. Psychiatry*, 138:1-13, 1981.

Table 4

Indicators in the Literature Not Supported by Expert/Practitioner Panels

Indicator	Bielski and Friedel	Nelson and Charney	Experts			Practitioners		
			% +	% –	%Non-indicator	% +	% –	%Non-indicator
Insidious onset	+	---	18	21	61	56	36	8
Agitated	+	mod. +	43	29	29	73	22	5
Delusional	mod. –	mod. –	0	75	25	30	63	7
Abnormal MHPG	+	---	39	0	61	54	24	22
Hypochondriasis	–	---	18	39	43	42	47	11
Somatic anxiety	–	---	18	25	57	66	27	7
Rejection sensitivity	–	---	3	43	54	64	31	5

Table 5

Expert and Practitioner Opposing Views

Indicator	Expert Panel	Practitioner Panel
Irritable	25% +	79% +
Somatic anxiety	18% +	66% +
Rejection sensitivity	3% +	64% +
Blames others	0% +	76% +
Craving for sweets	21% –	75% –

Table 6

Items of Greatest and Least Agreement

Greatest Agreement	Least Agreement
Weight loss	Agitated
Early morning awakening	Hypochondriasis
Psychomotor retardation	Blames others
Anhedonia	Rejection sensitivity
Anorexia	Somatic anxiety
Self-Reproach (blames self)	Irritability
	Craving for sweets

Areas of Disagreement

Table 4 shows a series of items alluded to in the literature which are either contradicted (insidious onset) or not substantially supported by panel responses.

Marked response differences between expe and practitioner panels are noted with respect t items listed in Table 5. All of these items have ap peared in the literature as descriptive of "atypica depression" and attempts have been made t associate them with positive response t monoamine oxidase inhibitors (MAOIs).

In reviewing these data, it is interesting to di tinguish items of greatest and least agreemen Table 6 displays the six items which stimulate th most consistent responses, and the seven item which stimulate the most diverse responses. Th diversity of response to these latter items ma serve to identify areas where research might b most useful in improving our ability to distinguis TCA responders and nonresponders. Conversely there seems to be little need to further documen the indicative value of weight loss, early morning awakening, psychomotor retardation, anhedonia anorexia, or self-reproach.

Comment on Individual Items

"Abnormal MHPG"—Recent research which tends to devalue MHPG as an indicator seems not to have penetrated the practitioner panel as well as it has the expert panel.

"Precipitant".—So few experts value the presence or absence of a precipitant to episode as a response indicator that it might be worthwhile to counsel practitioners to ignore the matter.

"Blames other"—This item produced the greatest net variance between expert and practitioner opinion in that practitioners felt it was a positive indicator and the experts felt it was worthless.

"Craving for sweets" – Much more significance as a nonresponse indicator is ascribed by practitioners than by experts. (75/21%)

"Delusional" – The relatively high valuation of this item as a nonresponse indicator may be impeding the concurrent use of TCA and a neuroleptic in the treatment of depression with delusions. Recent literature supports concurrent TCA/neuroleptic therapy as the treatment of choice.

Effects of Membrane Fluidity on Secretion and Receptor Stimulation

Fulton T. Crews, Ph.D.[1]

Introduction

The secretion of hormones and neurotransmitters as well as receptor mediated signal transduction are processes involving membranes. The initial secretory event involves a stimulus which causes a change in membrane permeability and/or other factors which lead to an increase in the intraneuronal calcium concentration. The increase in intraneuronal calcium concentration activates exocytosis, i.e., a mechanism where the membrane of the transmitter containing granule fuses with the neuronal plasma membrane releasing the granule contents extracellularly. This change in membrane permeability, which is necessary for secretion, is dependent on a change in membrane properties.

Once hormones or neurotransmitters are released, they carry out their specific functions by interacting with nerves or other target tissues. The initial event is the recognition of the hormone or transmitter by a receptor macromolecule on the outer surface of the cell membrane. The binding of the transmitter to its receptor then triggers a series of complex chemical and physical reactions in the membrane which permits the cell to carry out its specific function. Each of these reactions, i.e., receptor binding and coupling to ion channels and/or enzymes, is dependent on a suitable membrane environment. Thus, the metabolism of lipids as well as the lipid composition of the membrane plays an important role in the transduction of neurotransmitter, hormone, and other signals through the cell membrane.

[1]Department of Pharmacology, University of Florida College of Medicine, Gainesville, FL 32610.

Method

Membrane Fluidity

According to the now generally accepted fluid-mosaic model of membrane structure (Singer & Nicolson 1972), integral membrane proteins have hydrophobic ends embedded in the lipid matrix of the membrane which is at least in some parts fluid. The fluid properties of the lipid matrix have been suggested to play an important role in membrane transport (Coleman 1973), enzyme activity (Melchoir & Stein 1976), and other cell functions including receptor binding and stimulation (Rimon et al. 1978). Many membrane-bound enzymes and receptors have several subunits which interact within the membrane. Thus, the rate of subunit diffusion, rotation, and collision, as well as the maximal activity of enzymes, can be directly effected by the fluid properties of the lipid matrix in the membrane.

Phospholipid Methylation and Membrane Fluidity

Recent studies on enzymes altering membrane fluidity have centered on two methyltransferase enzymes that methylate phosphatidylethanolamine to form phosphatidylcholine. Although the methylation pathway is a minor pathway for the synthesis of phosphatidylcholine, evidence suggests that it is involved in both secretion and receptor-mediated membrane signal transduction. The two phospholipid methyltransferases have only recently been found to be present in rat brain and have their highest specific activity in the synaptosomal plasma membrane (Crews et al. 1980a; Mozzi & Porcellati 1979). The first enzyme, phospholipid methyltransferase I (PMT I), methylates phosphatidylethanolamine one time to form phosphatidyl-N-monomethyl-ethanolamine. PMT I has an optimum pH of 7.5 and a low ap-

parent K_m for S-adenosyl-L-methionine (SAM), the methyl donor. The second enzyme, phospholipid methyltransferase II (PMT II), catalyzes two successive methylations of phosphatidyl-N-monomethyl-ethanolamine to form phosphatidylcholine. PMT II has an optimum pH of 10.5, a high apparent K_m for SAM, and can be differentially solubilized by sonication. These observations suggest that the synaptosomal fraction of rat brain contains at least two methyltransferases which catalyze the synthesis of phosphatidylcholine. Blusztajn et al. (1979) have demonstrated the formation of phosphatidylcholine by the methylation pathway in calf caudate nucleus. In addition, this group has demonstrated the *in vitro* formation of free choline from phosphatidylcholine synthesized through the methylation pathway (Blusztajn & Wurtman 1981). Since these enzymes have been shown to affect transmitter-receptor stimulation in erythrocytes (Hirata et al. 1979b), astrocytoma cells (Strittmatter et al. 1979), and many other cell types (Hirata & Axelrod 1980), it seems likely they are involved in synaptic transmission.

Evidence for the asymmetric localization of phospholipid methyltransferases in synaptosome membranes has been obtained by selective proteolytic digestion using trypsin in intact and lysed synaptosomes (Crews et al. 1980c). Trypsin treatment caused a small reduction, about 13 percent, in PMT I activity in intact synaptosomes, while in lysed synaptosomes it destroyed 83 percent of the activity. This suggests PMT I mainly faces the cytoplasmic side of the plasma membrane where trypsin cannot penetrate. Trypsin treatment reduced PMT II activity by 57 percent in intact synaptosomes, and by 95 percent in lysed synaptosomes (Figure 1). The loss of PMT II in intact synaptosomes after trypsin treatment represents the fraction of the enzyme localized on the exterior side of the plasma membrane and indicates that PMT II is mainly present on the outer surface of the membrane. The additional loss of PMT II activity in lysed preparations probably represents PMT II present on vesicles, mitochondria, and other intrasynaptosomal particles.

Similar experiments using phospholipase C suggested that in intact synaptosomes phosphatidyl-N-monomethylethanolamine is buried within the membrane or located on the cytoplasmic side, whereas phosphatidylcholine and phosphatidyl-N,N-dimethylethanolamine ar exposed to the outer surface of the membran (Crews et al. 1980c). The phospholipid meth transferase enzymes have also been found to b asymmetrically distributed in liver microsoma membranes (Higgins 1981) and in rat erythrocyt ghosts (Hirata & Axelrod 1978a). These data sug gest the stepwise methylation and translocation o a fraction of the methylated phospholipids fro the cytoplasmic side to the outside of the mem brane (Figure 2).

The methylation and rapid vectorial rearrange ment of phospholipids has been shown to affec membrane fluidity. Using varying concentration of SAM, it was observed in rat erythrocyte ghost that the membrane viscosity, as measured b fluorescent polarization, using diphenylhe atriene (DPH), decreased in parallel with the syn thesis of phosphatidyl-N-monomethylethanol amine (Hirata & Axelrod 1978b). Other studie on chicken erythrocytes have found that con canavalin A will increase phospholipid methyla tion and simultaneously decrease membran viscosity (Nakajima et al. 1981). This study use the electron spin resonance spectra of a stearic acid spin label to estimate membrane viscosit and found that methylation inhibitors could bloc the concanavalin A-induced change in fluidity These studies suggest that the methylation o phosphatidylethanolamine and the rapid translocation of the methylated phospholipid ha an important influence on membrane fluidity.

Phospholipid Methylation, Ca^{2+} Flux and Exocytosis

Mast cells and basophils have been used t study the cellular mechanisms involved in secre tion (Douglas 1978; Kazimiercyak & Diamant 1978). The normal stimulus for mast cell secretion is the reaction of a specific antigen with an tibodies, i.e., immunoglobulin E (IgE), which are bound to the cell surface. Mast cells exposed to antigen accumulate $^{45}Ca^{2+}$. Furthermore, antigen stimulated $^{45}Ca^{2+}$ accumulation occurs even when the secretory response is inhibited by the cell being deprived of energy (Foreman et al. 1977), thereby supporting the hypothesis that calcium in flux is an early event in the secretory response

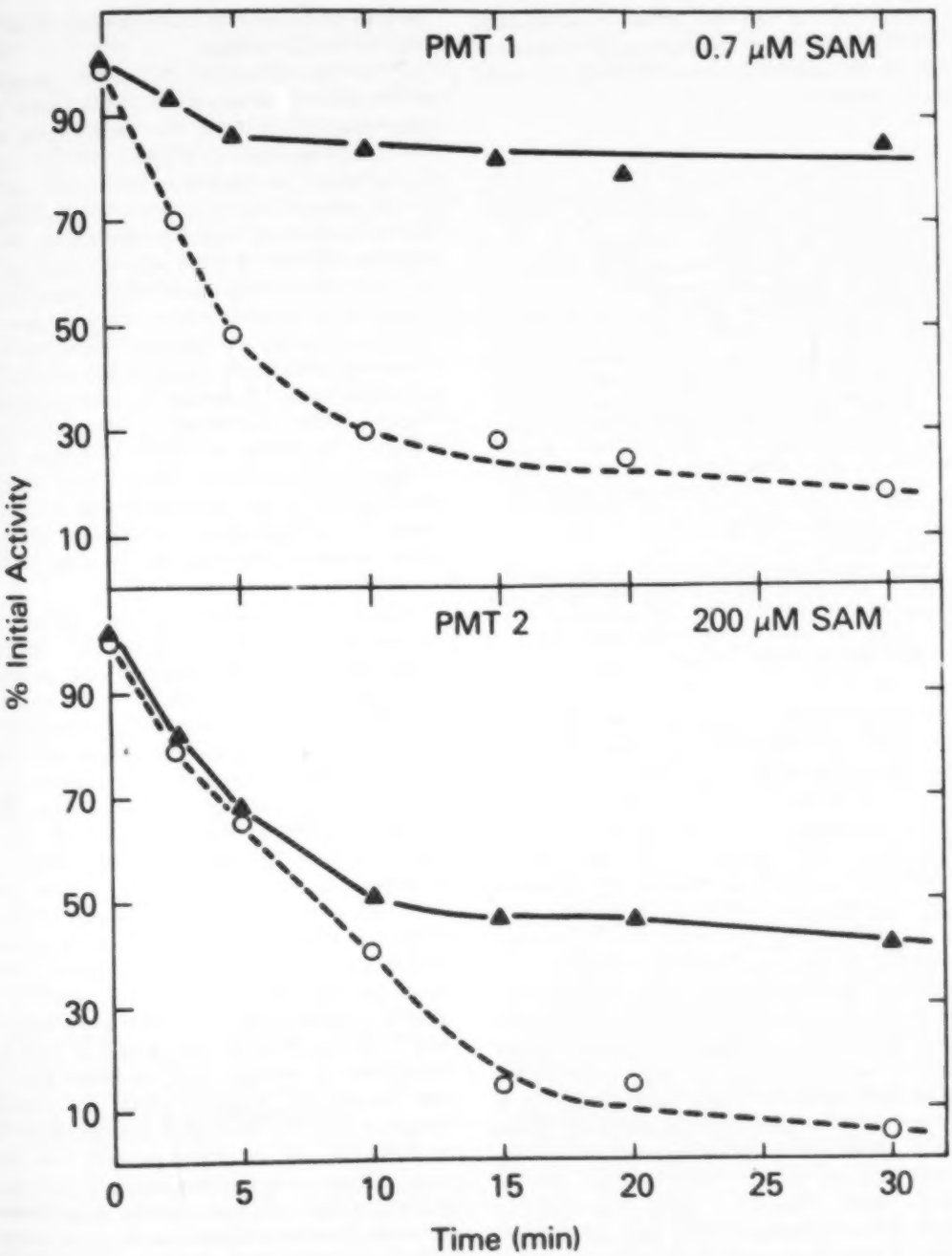

FIGURE 1. Effects of Trypsin Treatment on Lysed and Intact Synaptosomes. Synaptosomes (20 mg of protein) were incubated with trypsin, 1 mg/ml, for various periods of time. At various times, the reaction was stopped with buffer containing 5 mg/ml pancreatic trypsin inhibitor with 2 percent nonident and assayed for phospholipid methyltransferase I (PMT I) or phospholipid methyltransferase (PMT II) activity as described in Crews et al. (1980c). (▲—▲) Intact synaptosomes, (○—○) lysed synaptosomes.

The mechanism of calcium influx is particularly important, since many endogenous regulators of release are thought to act by inhibiting the initial influx of calcium.

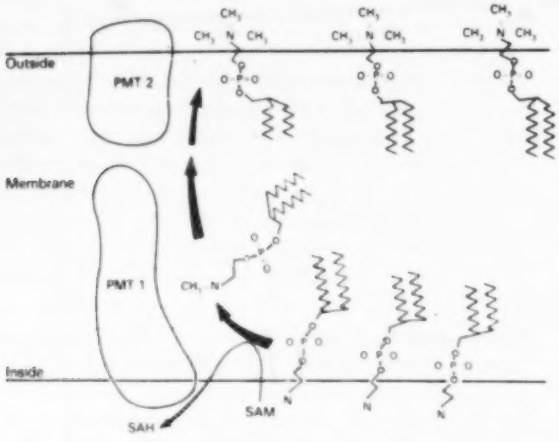

FIGURE 2. Schematic Diagram of Methylation and Translocation of Phospholipids in Synaptosomal Membranes. SAM is S-adenosyl-L-methionine, SAH is S-adenosyl-L-homocysteine.

The relationship between phospholipid methylation and histamine release was first studied using rat mast cells. Concanavalin A (Con A), a lectin which binds membrane glycoproteins (Siraganian 1976) was initially used to stimulate the secretion of histamine. Stimulating rat mast cells with Con A resulted in a rapid increase in methylated phospholipids which was followed by the release of histamine (Hirata et al. 1979a). After about 3 minutes, there was a fall in the methylated phospholipids suggesting further metabolism of these lipids. More recent studies on phospholipid methylation have used antibodies raised against IgE receptors on rat basophilic leukemia cells (anti-RBL). It is known that $F(ab')_2$ fragments of anti-RBL cause an influx of $^{45}Ca^{2+}$ and release histamine by bridging IgE receptors. $F(ab')_2$ fragments of anti-RBL also induce a rapid increase in phospholipid methylation which precedes $^{45}Ca^{2+}$ influx and histamine release (Ishizaka et al. 1980). Monovalent Fab' fragments failed to increase phospholipid methylation, induce $^{45}Ca^{2+}$ uptake, and release histamine. These findings suggest bridging of IgE receptors is necessary to initiate phospholipid methylation, $^{45}Ca^{2+}$ in[illegible] and histamine release.

The relationship between phospholi[illegible] methylation and secretion of histamine was [illegible] ther established using the methylation inhibi[illegible] 3-deazaadenosine (3-DZA). 3-DZA inhibi[illegible] phospholipid methylation and histamine rele[illegible] in an almost identical concentration-dependen[illegible] manner whereas other methylations were on[illegible] slightly affected. 3-DZA also blocked the rele[illegible] of [^{14}C]-arachidonic acid from prelabeled c[illegible] (Crews et al. 1980b). More recent studies on RB[illegible] cells have shown that antigen stimulation of l[illegible] sensitized cells results in an influx of $^{45}Ca^{2+}$ whi[illegible] precedes both histamine and arachidonic ac[illegible] release. When methylation was inhibited wi[illegible] 3-DZA, the influx of $^{45}Ca^{2+}$ was also inhibi[illegible] (Figure 3) (Crews et al. 1981). These findings a[illegible] consistent with the hypothesis that the initial i[illegible] crease in phospholipid methylation alters me[illegible] brane viscosity following the opening of the Ca[illegible] channel.

Additional evidence for the critical role [illegible] phospholipid methylation in Ca^{2+} influx a[illegible] histamine release was obtained with mutant RB[illegible] cells (McGivney et al. 1981). Two variant clon[illegible] of RBL cells were found which in response to a[illegible] tigen did not release histamine and had [illegible] calcium influx. However, stimulation with t[illegible] calcium ionophore did induce calcium flux a[illegible] histamine release. Both mutant cell lines we[illegible] found to have IgE receptors suggesting a defe[illegible] between the receptor and the calcium channe[illegible] One cell line was found to have PMT I a[illegible] almost no PMT II activity. A second variant ha[illegible] PMT II activity and no PMT I activity. Fusion [illegible] each cell line at a ratio of 1:1 resulted in th[illegible] growth of independent hybrids. Hybrids had no[illegible] mal levels of PMT I and PMT II activity an[illegible] responded to antigen-IgE mediated Ca^{2+} infl[illegible] and histamine release. Thus, by fusing tw[illegible] nonsecreting cell lines which lacked either PMT[illegible] or PMT II, the secretory process was reconst[illegible] tuted. These observations indicate that the cro[illegible] linking of IgE receptors results in an increase [illegible] both phospholipid methytransferases which the[illegible] allows an influx of Ca^{2+}.

The data suggest the following hypothe[illegible] (Figure 4): Antigen stimulation of the cells cro[illegible] links and aggregates IgE receptors which increa[illegible] the methylation of phospholipids resulting in

decrease in membrane viscosity. This decrease in viscosity probably occurs primarily in a specific domain where receptors, the phospholipid methyltransferases, the calcium ion channel, and other enzymes are localized. The change in viscosity could allow the opening of the Ca^{2+} channel. Thus, rapid changes lipid metabolism may alter the membrane fluidity in a highly localized domain within the membrane and thereby cause changes in the activity and coupling of proteins within this domain.

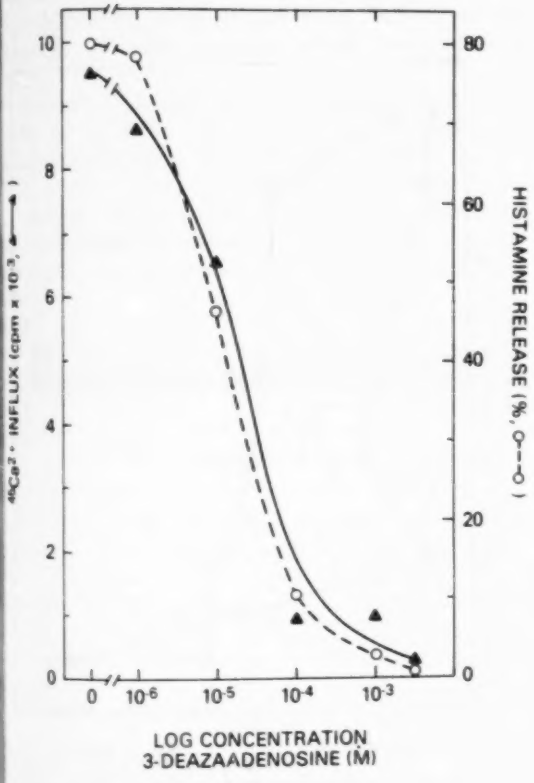

FIGURE 3. Effects of Various Concentrations of 3-Deazaadenosine (3-DZA) and Homocysteine Thiolactone on $^{45}Ca^{2+}$ Flux and Histamine Release. Rat basophilic leukemic cells (2×10^6 cells/well) sensitized with ovalbumin specific IgE were preincubated with various concentrations of 3-DZA and 2×10^{-4} M homocysteine thiolactone for 90 min. Cells were challenged with 10 μg/ml ovalbumin for 30 min. as described in Crews et al. (1981a).

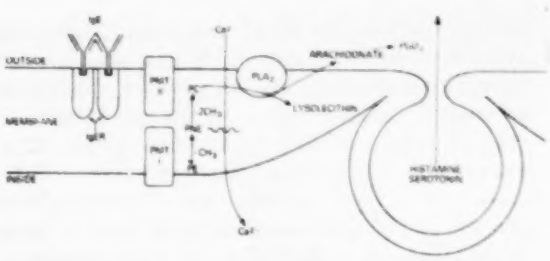

FIGURE 4. Schematic Diagram of Events During Antigen IgE Mediated Stimulation of Histamine and Arachidonic Acid Release. IgE is immunoglobin E and IgER is immunoglobin E Receptor. PE is phosphotidylethylnolamine which is methylated to PNE, i.e., phosphatidyl-N-monomethylmethanolamine, which would alter local membrane microviscosity allowing calcium influx. PC is phosphatidylcholine which can be hydrolyzed by PLA_2, i.e., phospholipase A_2 to lysolecithin, and arachidonate which is metabolized to PGD2, postaglandin D2.

Cholesterol/Phospholipid Molar Ratio and Membrane Fluidity

Although receptor stimulation may rapidly alter membrane fluid properties, the viscosity of the membrane is also affected by relatively low changes in composition. One change in composition that is known to alter membrane viscosity is the cholesterol to phospholipid molar ratio (C/P ratio). The interaction of the rigid backbone of cholesterol with phospholipid acyl chains increases the degree of order and restricts movement in the membrane interior (Cantor & Schimmel 1980). This increased order tends to increase viscosity (i.e., decrease fluidity), to abolish any phase transitions in membrane phospholipids and to alter the rotational freedom and position of proteins within the membrane lipid matrix (Shinitzky & Inbar 1976).

Studies of the synaptosomal plasma membrane (SPM) prepared from rats treated with ethanol have found changes in the C/P ratio. Ethanol and other anesthetics are thought to affect the nervous system by disrupting excitable membranes (Seeman 1972). This suggested that tolerance and physical dependence upon ethanol could be the result of an alteration in neuronal membranes during chronic exposure. The SPM from control rats, rats acutely treated with ethanol, rats dependent and intoxicated with ethanol, i.e., pro-

dromal dependent rats, and rats undergoing ethanol withdrawal were prepared and the C/P ratio determined (Crews, Majchrowicz, & Meeks, submitted). There was a significant increase in the C/P ratio of SPM from rats dependent and intoxicated with ethanol as compared to the SPM of control and rats acutely treated with ethanol (Figure 5). Cholesterol incorporation into membranes has been shown to increase membrane organization (Shinitzky & Berenholz 1978). An increased C/P ratio has also been found in the membranes of ethanol tolerant mice (Chin et al. 1978). Synaptic membranes prepared from tolerant mice are resistant to ethanol-induced fluidization in vitro, i.e., they have become tolerant to the disruptive effects of ethanol (Chin & Goldstein 1977). The disruptive affects ethanol on membranes are to some extent o posite to those of cholesterol. Cells may respo to the disruptive effects of ethanol by increasi the C/P ratio in their membranes. It is possib that under certain conditions cells can regula their membrane fluidity by altering the C/P rati Certainly, the evidence suggests that tolerano and dependence to ethanol are related to alter tions in nerve cell membrane organization an composition.

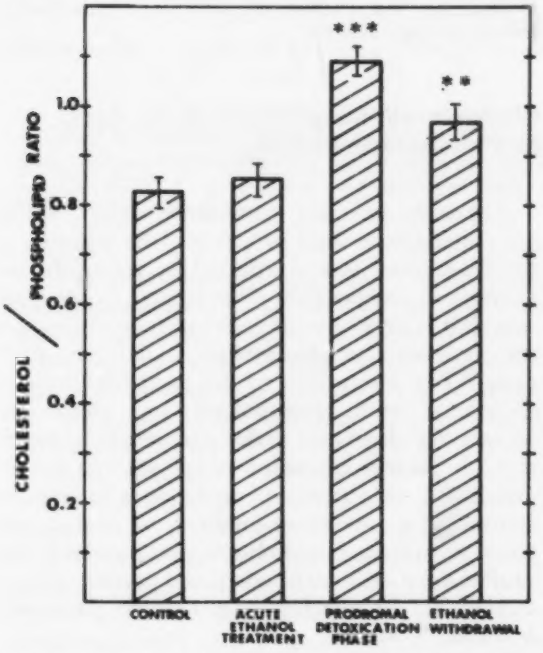

FIGURE 5. The Cholesterol/Phospholipid Molar Ratio of SPM Prepared from Rats after Various Alcohol Treatments. Controls were treated with water. Acute ethanol treatment involved a group of nonfasted animals given a single dose of ethanol (5 g/kg) 4 hrs prior to sacrifice. Prodromal detoxication phase group consisted of animals rendered physically dependent upon ethanol but were sacrificed while still intoxicated. The animals undergoing ethanol withdrawal syndrome were treated with ethanol as the prodromal group and were then decapitated at least 6 hrs after the onset of overt signs and symptoms of the ethanol withdrawal syndrome as described by Majchrowicz (1975).

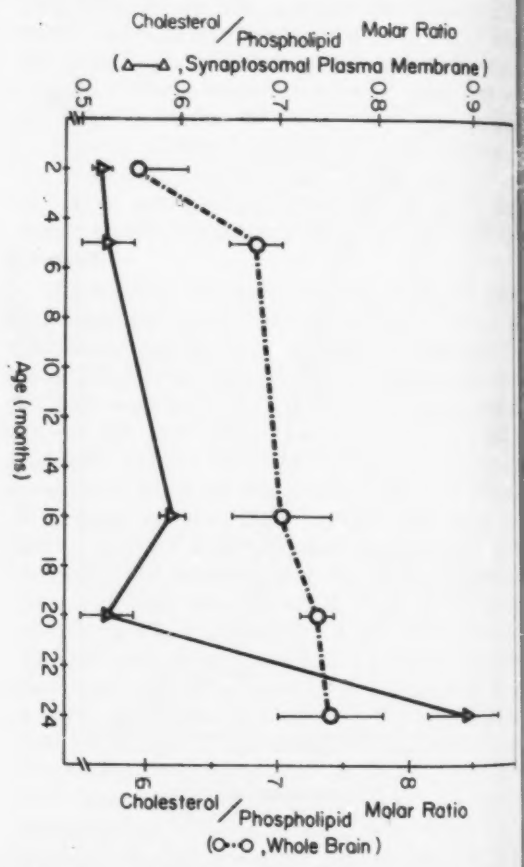

FIGURE 6. Cholesterol/Phospholipid Molar Ratio i Whole Rat Brain and in Purified Synaptosomal Plasm Membrane. Rats of various ages were decapitated an their brains rapidly frozen. On the day of analysis, brain were thawed and homogenized in 0.32 M sucrose. An ali quote was taken to determine total cholesterol an phospholipid content. Synaptosomal plasma membran were prepared as described by Jones and Matus (197 and the content of cholesterol and phospholipid deter mined.

In addition to the ethanol-induced changes in the C/P ratio of SPM, we have found that during aging there are changes in membrane C/P ratio. The SPM from rats of various ages was prepared and its lipid composition compared to that of whole brain. In whole brain the C/P ratio increased in young rats between 2 and 5 months of age and then remained relatively constant. In contrast, the C/P ratio of SPM changed very little in rats 2 to 20 months of age. However, the C/P ratio in SPM of rats 24 months of age was increased almost twofold over the C/P ratio of SPM in 20-month-old rats (Figure 6). This alteration in the SPM composition would be expected to alter synaptic transmission and may be related to changes in brain function which occur during aging.

To investigate the effects of changes in the C/P ratio on synaptic transmission, we studied carbachol stimulation of pyramidal neurons in the CA1 region of rat hippocampal brain slices. Since cholesterol transfer occurs between proteins rich in cholesterol to membranes containing smaller amounts, we incorporated cholesterol into hippocampal slices by perfusing them with buffered Yamamoto's solution containing 1 percent bovine serum albumin saturated with cholesterol (Figure 7). Recordings were made through a glass micropipette filled with 3 M NaCl saturated with fast green dye as described previously (Camacho & Phillips 1982). The cholineric agonist carbachol consistently excited cells in the hippocampus. Atropine blocked carbachol, suggesting muscarinic receptor mediated stimulation of firing. Incorporation of cholesterol markedly reduced carbachol induced firing of the hippocampal purkinje cells (Figure 7). When the response to carbachol was almost completely inhibited, perfusion buffers were changed and the cholesterol was washed out of the slice by perfusion with buffer containing albumin alone (Figure 8). Removal of cholesterol restored the carbachol response to near control levels. Characteristic action potentials were used to establish the identity of the cell, i.e., that the return of firing occurred in the same cell. It is possible that cholesterol incorporation disrupts the binding and/or stimulus transduction of acetylcholine like agents in neuronal membranes.

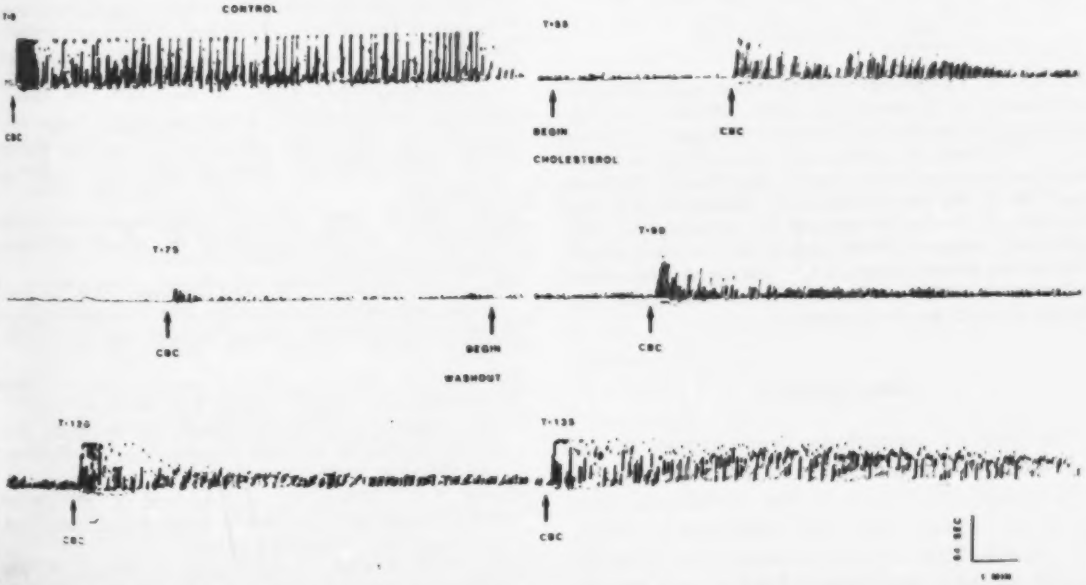

FIGURE 7. Effects of Cholesterol Incorporation on Carbachol (CBC) Stimulation of Hippocampal Pyramidal Cells. Slices of rat hippocampus were sandwiched between nylon netting. Recordings were made through a glass micropipette from hippocampal pyramidal cells in CA1. Carbachol (CBC) was added at the times indicated. Slices were constantly perfused at a rate 5 ml/min with Yamamoto's buffer containing 1% bovine serum albumin. A typical control response is shown at time O (i.e., T=0). Typical responses could be obtained for 4 to 6 hours. Arrows show that beginning of perfusion with buffer saturated with cholesterol and the beginning of cholesterol wash out, i.e., buffer with no cholesterol.

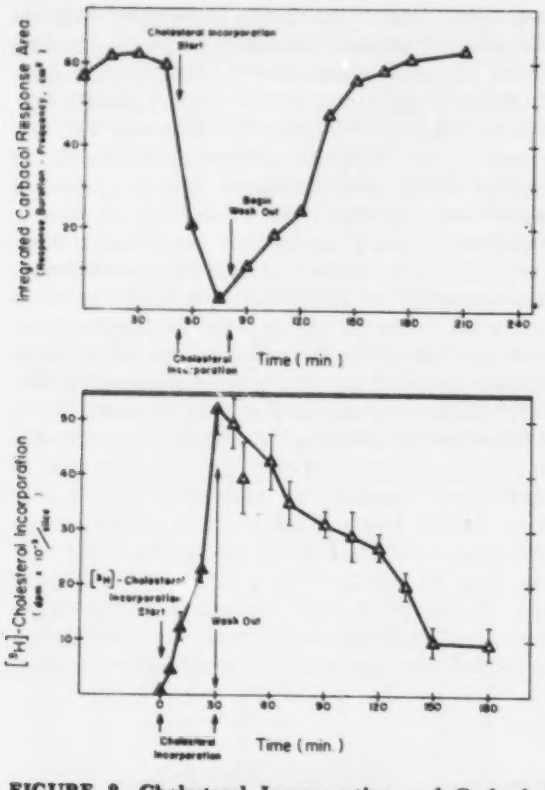

FIGURE 8. Cholesterol Incorporation and Carbachol Stimulation of Hippocampal Cells. Slices of rat hippocampus were perfused as described in Figure 8. The upper graph shows the intergraded area of the carbachol stimulated response from a typical experiment. The lower graph shows the incorporation of cholesterol into hippocampal slices was determined by perfusing the slices with media containing [^{3}H]-cholesterol (1 uCi/ml) attached to bovine serum albumin where indicated. Wash out of cholesterol involved perfusion with the same buffer containing albumin but no cholesterol.

Conclusions

The role of membrane organization in cell function is just beginning to be understood.

The fluid properties of the membrane lipid matrix has a major effect on membrane function. The phospholipid methyltransferase enzymes can rapidly increase membrane fluidity and thereby alter certain cellular processes. This rapid change in viscosity is thought to occur in a localized domain containing receptors, ion channels, and various other proteins important for membrane signal transduction. It is possible that many transmitters and hormones transmit their signa by rapidly changing membrane fluidity.

The physiological and pharmacological factor that alter membrane fluidity by changing the C/P ratio are much slower than the rapid changes wit phospholipid methylation. In addition, it is no clear whether changes in bulk fluidity, the forma tion of distinct lipid domains, or some other effec of cholesterol on membrane structure, is respons ble for the physiological changes that occur i cholesterol enriched membranes. However, it i clear that the regulation of cholesterol and phospholipid content provides the cell with mor potential ways to alter cell membrane function Further studies on the regulation as well as the localization of the various membrane fluid do mains are likely to be exciting and physiologically important studies on the functions of cell mem branes.

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A Study of the Metabolism of Des-Tyrosine-γ-Endorphin Using an Improved HPLC System[1]

Hans Schoemaker, Ph.D.,[2] Andrew Chen, B.S.,[2] Thomas P. Davis, Ph.D.,[2] and Henry I. Yamamura, Ph.D.[2]

Introduction

In vitro proteolytic processing of β-endorphin (βE) by rat brain enzymes results in the formation of α-endorphin (αE, βE 1-16), γ-endorphin (γE, βE 1-17), and their non-opiate analogs des-tyrosine[1]-α-endorphin (DTαE, βE 2-16) and des-tyrosine[1]-γ-endorphin (DTγE, βE 2-17) (Austen et al. 1977; Burbach et al. 1980a). These peptide fragments, the presence of which has recently been confirmed in the rat (Verhoef et al. 1982) and human brain (Van Ree & De Wied 1981), differentially affect central mechanisms of adaptive behavior (Bohus 1981; De Wied et al. 1978). Consequently, βE homeostasis has been implicated in various aspects of behavioral adaptation (De Wied et al. 1978; Van Ree & De Wied 1981). Furthermore, it has been proposed that disturbances in βE homeostasis could be of etiological significance in psychopathological disorders (Berger & Barchas 1981; Bloom et al. 1976; De Wied 1979).

Several γE related peptides, and most notably DTγE, have shown neuroleptic-like activity in a variety of behavioral paradigms (Davis et al. 1981; De Wied et al. 1978; Dorsa et al. 1979). Clinical studies also indicate that DTγE may be of therapeutic value in the treatment of schizophrenia (Verhoeven et al. 1978, 1981). Like classical neuroleptics, DTγE decreases *in* [3]H-spiperone binding in the rat striatum and nucleus accumbens (Pedigo et al. 1979b), which is indicative of an inhibitory effect on the postsynaptic dopamine receptor. Since DTγE fails to affect the *in vitro* binding of radiolabeled agonists and antagonists to the dopamine receptor (Pedigo et al. 1979a; Van Ree et al. 1978), it was suggested that DTγE may exert its selective neuroleptic-like effect *in vivo* through an active metabolite (De Wied et al. 1980; Pedigo et al. 1979b). In the present study, the *in vitro* metabolism of DTγE was examined with the use of a sensitive and selective high performance liquid chromatographic (HPLC) system that allows for a rapid and efficient separation of βE peptide fragments (Davis et al. 1982).

Method

The *in vitro* metabolism of DTγE was studied by incubating DTγE in a final concentration of 1-2 mg/ml with whole rat brain homogenates (50 mg tissue/ml), rat striatal slices (0.5 × 0.5 × 0.5 mm, approximately 25 mg tissue/ml), and homogenates of the human caudate nucleus. Postmortem human brain samples were obtained at autopsy from subjects with no known neurological or mental disease. Autopsy took place within 3.5-16 hours after death, and tissues were stored at -80°C for 4-6 months before use. After incubation at 37°C in 50 mM sodium potassium phosphate buffer (81 mM Na^+, 9 mM K^+), pH 7.4, samples were boiled for 10 minutes at 100°C and centrifuged at 15,000 × g for 15 minutes. The clear supernatant was stored at -20°C until HPLC analysis (Davis et al. 1982, Schoemaker et al. 1982).

The HPLC analysis was performed using two Model 6000A pumps and a Model 600 Solvent Programmer (Waters Associates, Milford, Mass.). Eluting peptides were detected using a Perkin-Elmer LC-65T variable wavelength UV detector (Perkin-Elmer, Norwalk, Conn.) set at 210 nm. Baseline drift due to mobile phase refractive index changes was corrected for using an Axiom Model 301-99 Data Saver (Cole Scientific, Calabasas, Cal.). Recording and peak quantification was accomplished using a Hewlett-Packard 3390A integrator and strip chart recorder. Peptides were separated using a Beckman Ultrasphere

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[2]Departments of Pharmacology, Biochemistry, and Psychiatry and the Arizona Research Laboratories, University of Arizona Health Sciences Center, Tucson AZ 85724.

Correspondence may be addressed to: Dr. Henry I. Yamamura, Department of Pharmacology, University of Arizona Health Sciences Center, Tucson, AZ 85724.

ODS 5μ column maintained at 40°C, and a curve-linear gradient of acetonitrile against 0.1 M NaH_2PO_4 (pH 2.1) from 18 to 30 percent over 40 minutes at a flow rate of 2.0 ml/minute. Peptide quantification was based on the external standard method of analysis using reference peptides which had previously been tested for purity by chromatographic methods.

Endorphin fragments were generously donated by Drs. N.C. Ling (The Salk Institute), and H.M. Greven and J.W. van Nispen (Organon Int.).

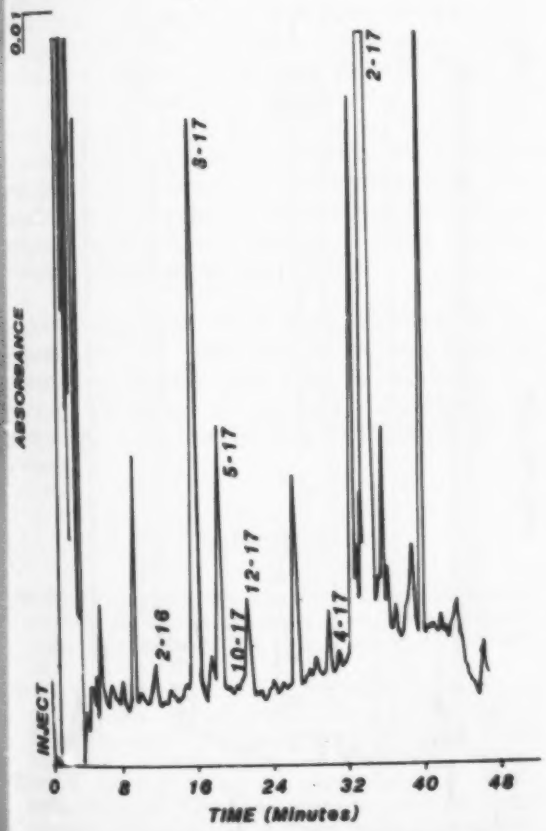

FIGURE 1. Digestive pattern of DTγE metabolism upon incubation with whole rat brain homogenates as determined by HPLC analysis. DTγE (1.5 mg/ml) was incubated with a 5 percent homogenate of whole rat brain for 30 min. at 37°C. After boiling of the sample for 10 min. to inactivate peptidase activity, and a 15 min. centrifugation at 15,000× g, the clear supernatant was directly used for HPLC analysis.

Results

The HPLC method employed in the present experiments results in a rapid and efficient separation of βE related peptide fragments. The detection limit under these conditions is 10 ng for each peptide (Davis et al. 1982).

A representative fragmentation pattern of the metabolism of DTγE upon incubation with rat brain homogenates for 30 minutes is shown in Figure 1. The major metabolite was identified as βE 6-17, whereas minor metabolites could be identified as βE 4-17, βE 5-17, βE 10-17, βE 12-17, and βE 2-16 (DTαE). After a 30-minute incubation, approximately 33 percent of the parent DTγE could be recovered. After incubation of DTγE with boiled homogenates for 30 minutes DTγE was recovered unchanged, indicating that breakdown is indeed enzymatic. Conversely, no peptide peaks could be detected in extracts of tissue incubated in the absence of exogenously added DTγE. Time-course experiments (Schoemaker et al. 1982) indicated that the decline in residual DTγE levels was monoexponential with a half life of 14-15 minutes. The major metabolite, βE 6-17, reaches a maximal level of about 30 percent of that of the parent peptide, DTγE, after 30 minutes of incubation. Maximal levels of βE 5-17 were observed after 15 minutes of incubation, and represented about 5 percent of the residual amount of DTγE at this time.

A qualitatively similar pattern of metabolism was found upon incubation of DTγE with rat striatal slices. Prior to incubation, the slices were thoroughly rinsed with 2 × 10 ml buffer in order to remove intracellular enzymes from those cells damaged during the preparation of the tissue. Figure 2 illustrates the metabolic pattern observed after incubation at 37°C for 120 minutes. Major metabolites were identified as βE 5-17 and βE 6-17, whereas minor amounts of βE 2-16, βE 4-17, βE 10-17, and βE 12-17 were also present.

In addition, *in vitro* DTγE metabolism was studied using homogenates of the human caudate nucleus. Metabolism was qualitatively similar to that observed in whole rat brain homogenates and rat striatal slices (Figure 3). Also in this case βE 6-17 emerged as the major metabolite. Moreover, the fragmentation pattern was virtually identical between the different subjects studied.

Discussion

The metabolism of DTγE upon incubation with whole rat brain homogenates, rat striatal slices, and homogenates of the human caudate nucleus was examined using a newly developed, sensitive and selective HPLC chromatographic system for βE fragments. In each tissue preparation studied, the enzymatic breakdown of DTγE proceeded in a qualitatively similar manner, and βE 6-17 constantly emerged as the major metabolite. The βE sequences 2-16, 4-17, 5-17, 10-17, and 12-17 were also present but in minor amounts. βE 6-17 was previously reported to be among the major metabolites associated with DTγE digestion by peptidase activity in synaptosomal plasma membranes (Burbach et al. 1980b). Interestingly, the major DTγE metabolite identified in this study, βE 6-17, is the shortest γE related peptide to retain the full spectrum of behavioral effects of DTγE (De Wied et al. 1980), including its putative antipsychotic activity (Verhoeven et al. 1981). Like DTγE, βE 6-17 fails to affect the ^{3}H-spiperone labeled dopamine receptor *in vitro* (Pedigo et al. 1981; Schoemaker et al. 1982). Similarly, no inhibition of ^{3}H-spiperone binding to rat striatal membranes could be demonstrated for C-terminal fragments of DTγE up to βE 14-17 in concentrations of 10 μM (unpublished observations). It therefore seems unlikely that the inhibitory effect of DTγE on *in vivo* ^{3}H-spiperone binding in the rat striatum and nucleus accumbens (Pedigo et al. 1979b) arises from a direct interaction of the γ-type endorphins with the postsynaptic dopamine recep-

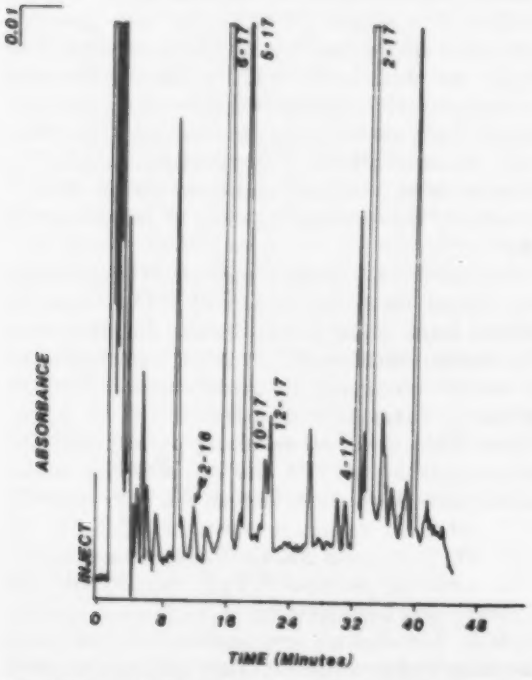

FIGURE 2. Digestive pattern of DTγE metabolism upon incubation with rat striatal slices. DTγE (1.5 mg/ml) was incubated with rat striatal slices (0.5 x 0.5 x 0.5 mm) for 120 min. at 37°C. Samples were prepared for HPLC analysis as described in Figure 1.

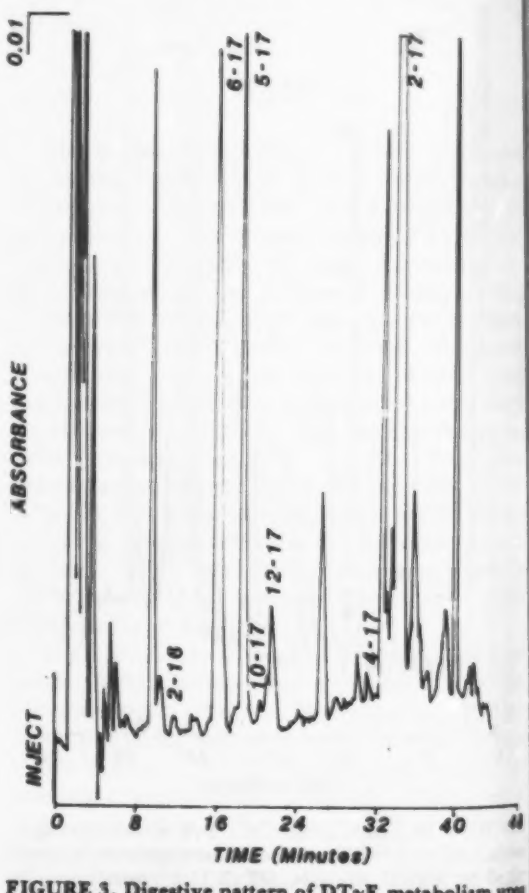

FIGURE 3. Digestive pattern of DTγE metabolism upon incubation with homogenates of the human caudate nucleus. DTγE (1.5 mg/ml) was incubated with a 5 percent homogenate of the human caudate nucleus for 30 min. at 37°C. The brain tissue sample had previously been stored at -80°C for 6 months.

ter. The possibility remains that DTγE alters dopaminergic activity in the mesolimbic and striatal pathways by an indirect effect on the postsynaptic dopamine receptor or through a presynaptic mechanism, as suggested by *in vitro* (Schoemaker & Nickolson 1980) and *in vivo* experiments (Davis et al. 1981; Nickolson 1981; Nickolson & Berendsen 1980; Van Ree & De Wied 1981).

Derangements in the balance of α-, β-, and γ-type endorphins in the human brain have been suggested to underly the etiology of schizophrenia (De Wied 1979). Thus, a relative excess of βE was hypothesized to result in the catatonic aspects of this disease, whereas an imbalance towards the α-type endorphins that show amphetamine-like behavioral activity (De Wied et al. 1978; Dorsa et al. 1979), would be prevalent in paranoid schizophrenia. The present findings that DTγE metabolism upon incubation with homogenates of the previously frozen human caudate nucleus proceeds similarly to that found using fresh rat brain tissues, suggest the feasibility of future studies directly addressing this hypothesis.

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enkephalin; that is, high concentrations diminished blastogenesis and low conentrations stimulate blastogenesis.

It is proposed that the enkephalins play a neuroendocrine role between the central nervous system and the pituitary-adrenal axis. In addition, it is proposed that the enkephalins released from the adrenals, in time of stress, stimulate the immune system.

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The Central Nervous System Control of the Immune System—Enkephalins: Antitumor Activities

Nicholas P. Plotnikoff, Ph.D.[1]

In 1979, Wybran, et al. reported that human blood T lymphocytes bear surface receptor-like structures for methionine-enkephalin. The present study explores the relationships between the central nervous system and the immune system.

The effects of leucine-enkephalin as well as the effects of methionine-enkephalin were studied in BDF mice inoculated with 1×10^4, 1×10^3, and 1×10^2, L1210 leukemia cells. An increase in survival time of the leucine-enkephalin treated mice was seen in mice inoculated with 1×10^2 L 1210 cells. Furthermore, the survivors managed to rechallenge to 1×10^4 cells. Higher doses of the enkephalins (30 mg/kg) were found to prolong survival of mice inoculated with 1×10^4 cells.

In addition, methionine enkephalin, in the presence of PHA, was found to stimulate lymphocyte blastogenesis at high molarities while diminishing (slightly) at low concentrations. The reverse appeared to be the case with leucine

[1]Department of Pharmacology, Oral Roberts University School of Medicine, Tulsa, OK 74171.

A Behavioral Study of the Changes in the CNS of Mice After Subchronic Treatment With the Dopamine Autoreceptor Agonist 3-PPP

Stephan Hjorth, B.Sc.[1], David Jackson, Ph.D.,[2] Arvid Carlsson, M.D.,[1] and Per Lindberg, Ph.D.[3]

Introduction

It is becoming increasingly evident that changes in receptor sensitivity contribute to the long-term homeostasis of synaptic function in the dopamine (DA) systems of the central nervous system. This property of receptors to change their sensitivity may be of key importance in the clinical efficacy of a number of drugs and in the development of side effects.

We have recently described the properties of a new DA receptor agonist, 3-(3-hydroxyphenyl)-N-n-propylpiperidine (3-PPP) (Hjorth et al. 1981). This compound exhibits a considerable selectivity for DA autoreceptors and, except in very high doses, is essentially devoid of other psychopharmacological properties. This unique profile makes 3-PPP of considerable theoretical interest, both in its own right and as a tool for use in psychopharmacological research. Some preliminary behavioral studies of the effects of 3-PPP administered subchronically to mice are reported here.

Method

Animals and Equipment

Male mice (18-24 g at the beginning of experimentation) of the N.M.R.I. strain (Anticimex, Stockholm) were kept at 25 ± 1° on a 12-hour light-dark cycle, with food and water *ad libitum*. The locomotor activity of groups of three mice was assessed in four "M/P" 40 Fc electronic motility meters (Motron Products, Stockholm). In all activity studies, except where otherwise stated, recordings were commenced 5 minutes after drug challenge.

Chronic Pretreatment

Each mouse was injected twice daily, between 7:45 and 9:30 a.m., and between 4:00 and 5:45, with 23.5 mg/kg of 3-PPP expressed as the base, but given as the hydrochloride salt. The pretreatment dose was chosen with reference to the depressant potency of 3-PPP, and after several preliminary experiments. The subchronic pretreatment schedule lasted for 5 days (10 injections) and behavioral assessments were made 15 to 25 hours after the last subchronic dose. Control animals received an injection of saline (0.2 ml) at the appropriate times each day. All injections were intraperitoneal (i.p.), with an injection volume of 10 ml/kg. In the text, the doses of drugs are expressed in terms of the salt forms, except 3-PPP which is expressed in terms of the base.

Statistical Methods

Statistical comparisons were made with a two-tailed Student's *t*-test, in some cases preceded by an analysis of variance.

Results

Acute Experiments

In naive mice, the selective dopamine (DA) autoreceptor agonist 3-PPP (3-(3-hydroxyphenyl)-N-n-propylpiperidine) produced a dose-dependent depression of locomotor activity (Figure 1).

The duration of action of the depression was short, with no significant depression being noted 1 or more hours after a dose of 23.5 mg/kg i.p. (Table 1).

[1]Department of Pharmacology, University of Göteborg, Sweden.
[2]Department of Pharmacology, University of Sydney, Australia.
[3]Org. Chem. Unit, Department of Pharmacology, University of Göteborg, Sweden.

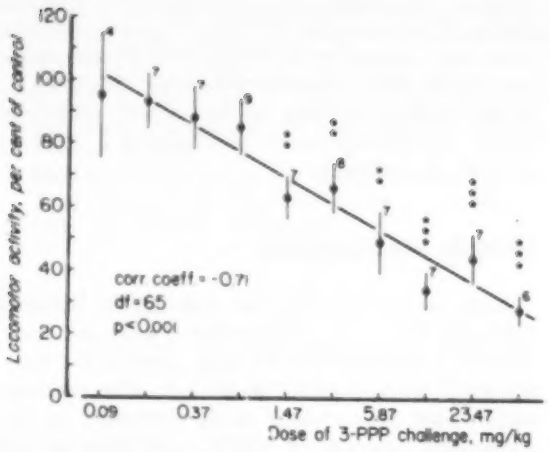

FIGURE 1. The effect of various doses of 3-PPP on the locomotor activity of groups of three mice. The data represent the means and standard errors of the activity in the 30 minutes beginning 5 minutes after injection, and each mean consists of 4 to 8 replicates. The line of best fit was calculated by regression analysis. $^{**}p<0.01$, $^{***}p<0.001$.

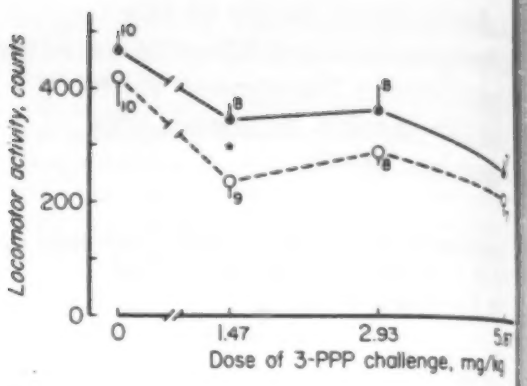

FIGURE 2. The effect of pretreatment of mice with 3-PPP (•—•) or vehicle (○—○) on the response to a challenge dose of 3-PPP. The data represent the means and standard errors of the activity from 5 to 50 minutes after beginning of the measurements. $^{*}p<0.05$ (for details see the text).

Subchronic Experiments

Mice, administered the drug twice daily (23.5 mg/kg i.p., in the morning and in the evening) for 5 days, were 15 to 25 hours after the last dose subsensitive to the locomotor depressant effects of a challenge with the same drug (Figure 2).

Table 1

The Effect of Different Treatment Times on the Locomotor Response of Mice to 23.5 mg/kg of 3-PPP

Treatment Time (h)	Treatment	Locomotor Activity (*N*)	
0	Saline	248 ± 8	(6)
	3-PPP	58 ± 14	(8)[a]
1	Saline	221 ± 21	(8)
	3-PPP	174 ± 10	(8)[b]
2	Saline	229 ± 13	(8)
	3-PPP	198 ± 12	(8)

[a] $p<0.001$.
[b] $p=0.086$ from the corresponding saline control.

Note: Locomotor activity was measured for 15 minutes either 0, 1, or 2 hours after injection of saline or 3-PPP. The locomotor activity is expressed as the counts per 15 minutes with standard error of the mean.

Table 2

The Effect of Challenge with Apomorphine (0.5 or 1.0 mg/kg) on the Locomotor Response of 3-PPP or Vehicle-Pretreated Mice Treated with Reserpine (10 mg/kg) and α-MT (250 mg/kg)

Dose of Apomorphine (mg/kg)	Locomotor Activity ± S.E.M. (*N*) 3-PPP-Pretreated	Vehicle-Pretreated
0	2 ± 1 (3)	3 ± 1 (3)
0.5	273 ± 38 (9)	262 ± 25 (9)
1.0	542 ± 34 (9)	563 ± 34 (9)

Note: The data represent the mean activities in the hour beginning 5 minutes after challenge together with the standard errors of the means.

There was no change in the sensitivity of postsynaptic DA- and α-adrenergic receptors, as assessed by the locomotor stimulant effects of apomorphine and apomorphine plus clonidine, respectively, in reserpine- and α-methyltyrosine-treated animals (Table 2 and Figure 3).

However, 3-PPP-pretreated mice were supersensitive to the activating effects of *d*-amphetamine, and this supersensitivity was blocked by reserpine pretreatment (Figure 4 and Table 3).

In naive mice, a low, DA-autoreceptor selective dose of haloperidol (25 μg/kg) potentiated the locomotor stimulant effects of *d*-amphetamine (Figure 5).

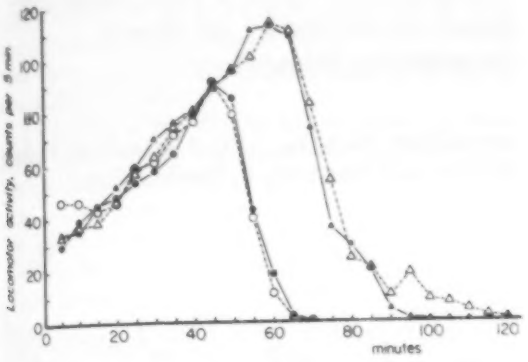

FIGURE 3. The effect of challenge with apomorphine (2 mg/kg) (circles) or apomorphine plus clonidine (2 mg/kg) (triangles) on the locomotor response of 3-PPP-pretreated (closed symbols) and vehicle-pretreated (open symbols) animals. Locomotor activity was assessed each 5 minutes, and the data represent the means of seven replicates. The standard errors of the means have been omitted for clarity, but in no case was there a significant difference in the response of the two groups to apomorphine challenge or to apomorphine plus clonidine challenge. The locomotor activities of animals challenged with saline or clonidine alone were essentially zero and have been omitted for clarity.

Table 3

Effect of Vehicle or Reserpine (10 mg/kg, 5 hv treatment) on the Response of 3-PPP- or Vehicle-Pretreated Mice to *d*-amphetamine (1.5 mg/kg) Challenge

Treatment	Challenge	Pretreatment Group: Vehicle	Pretreatment Group: 3-PPP
Vehicle	Saline	388 ± 56 (6)	376 ± 29 (6)[a]
	d-Amphetamine	737 ± 90 (8)	1277 ± 166 (9)[b]
Reserpine	Saline	12.3 (2)	8.5 (2)
	d-Amphetamine	223 ± 17 (9)	285 ± 44 (9)[a]

[a] Not significant ($p > 0.05$)
[b] $p < 0.05$ from the corresponding vehicle-pretreatment group.

Note: The data represent the mean locomotor activities in the two groups during the 90 minutes immediately following *d*-amphetamine or saline challenge. The standard error of the means are given, and the numbers in parentheses represent the number of replicates.

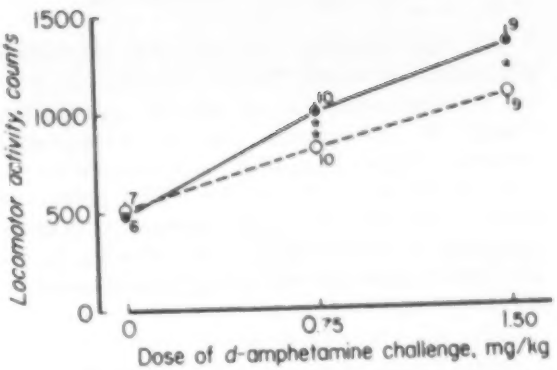

FIGURE 4. The effect of subchronic treatment with 3-PPP (or vehicle) on the locomotor response to *d*-amphetamine or saline challenge. The data represent the means and standard errors of the activity counts during the first hour of 6-10 replicates. •—•, 3-PPP-pretreated: ○—○ vehicle-pretreated. $^{*}p < 0.05$, $^{**}p < 0.01$.

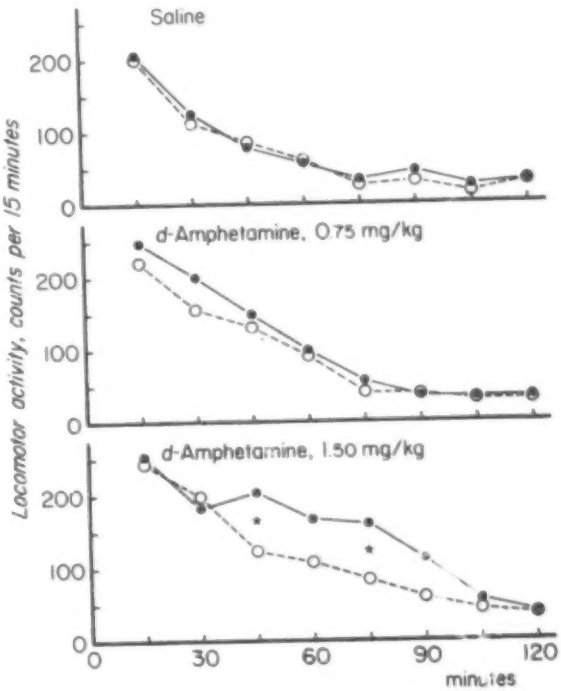

FIGURE 5. The effect of pretreatment of mice with haloperidol (25 μg/kg, 20 minutes •—•) or acid vehicle (○—○) on their response to challenge with saline or *d*-amphetamine. Locomotor activity was monitored each 15 minutes for 2 hours. The data represent the means of 7-22 replicates with the standard errors omitted for clarity. $^{*}p < 0.05$.

Summary and Conclusions

The data obtained indicate that subchronic pretreatment with 3-PPP procuded DA-autoreceptor subsensitivity with no concomitant change in postsynpatic DA- or α-adrenergic receptor sensitivity. The supersensitivity to *d*-amphetamine evident in the 3-PPP pretreated mice may be due to the DA autoreceptors being subsensitive, thus leading to a reduction in the feedback control exerted by the DA released by the *d*-amphetamine.

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Studies of Plasma Homovanillic Acid as an Index of Brain Dopamine Function[1]

Kenneth S. Kendler, M.D.,[2] John Y-K. Hsieh, Ph.D.,[2] and Kenneth L. Davis, M.D.[2]

In the rat, plasma levels of the dopamine (DA) metabolite homovanillic acid (HVA) change in parallel with brain levels of HVA after electrical stimulation, ablation of the brain DA system (Bacopoulos et al. 1979), and after administration of DA receptor-blocking neuroleptics (Bacopoulos et al. 1979; Kendler et al. 1981), and DA agonist drugs (Kendler et al. 1982). By selective inhibition of peripheral production of HVA by the drug debrisoquin, Kendler et al. (1981, 1982) showed that the alterations in plasma levels of HVA (pHVA) after DA blocking and agonist drugs were due largely or exclusively to the effect of the drugs on the brain. Based on these results and more limited studies in monkeys and man, pHVA has been proposed as a useful index of central DA function in human neuropsychiatric conditions. To further clarify the circumstances under which pHVA reflects brain DA function, the investigators examined the effects of a relevant behavioral stimulus, stress, and a relevant pharmacologic stimulus, probenecid, on central and plasma levels of HVA.

Approximately half of pHVA originates from sources other than the brain (Bacopoulos et al. 1979; Hoeldtke et al. 1974; Maas et al. 1979) probably from the sympathetic nervous system and the adrenal medulla. Stress increases plasma levels of catecholamines, including DA, several fold (Jindra et al. 1980; Van Loon et al. 1979). If appreciable amounts of these catecholamines were

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[2]Department of Psychiatry, Veterans Administration Medical Center, Bronx, NY 10468 and Mt. Sinai School of Medicine, New York, NY 10029.

Address correspondence to: Kenneth S. Kendler, M.D., VA Medical Center, 130 West Kingsbridge Road, Bronx, NY 10468.

metabolized to HVA, stress could induce a selective increase in the peripheral production of HVA that could obscure the relationship of pHVA to brain DA function.

To measure the rate of DA turnover in man, levels of HVA in the cerebrospinal fluid (CSF) have been measured before and after administration of the drug probenecid. Probenecid blocks the egress of HVA from CSF and brain and also inhibits the renal clearance of HVA from plasma (Faull et al. 1981). It is therefore of interest to determine whether plasma levels of HVA continue to correlate well with central HVA levels after administration of probenecid. Could a low dose of probenecid selectively block renal excretion of HVA without altering clearance of HVA from CSF and brain thereby permitting measurement of whole body production of HVA by measuring the rate of rise of pHVA?

Method

Stress Studies

Male, Sprague-Dawley rats, weighing 250-350 g, and food-deprived for 24 hours prior to sacrifice, were subject to one of three forms of stress: brief (4 minutes) ether stress, one 90-minute period of restraint stress, and five daily 150 minutes periods of restraint stress. Blood was obtained by open-chest cardiac puncture after which the brains were immediately removed and frozen on dry ice. Immediate decapitation with blood collected from the carotid arteries was used as a control for the brief ether stress. Since no difference was found between these two groups, open-chest cardiac puncture after brief ether anesthesia was used for both control and experimental animals in further studies.

Probenecid Studies

Fasted, male Sprague-Dawley rats were administered vehicle or probenecid (20,40,60, and 80 mg/kg) 4 hours prior to sacrifice. Plasma for HVA levels was obtained just prior to lumbar puncture in seven psychiatric patients after no pretreatment and again after the administration orally of probenecid 100 mg/kg over 24 hours.

Free HVA in brain and CSF was measured by high-performance liquid chromatography and in plasma by gas chromatography/mass spectrometry.

Results

Brief ether stress compared to controls sacrificed by immediate decapitation had no significant effect on either plasma or whole brain HVA concentrations (Table 1). Similarly, one episode of restraint stress did not significantly alter plasma or whole brain HVA concentrations (Table 2). However, repeated restraint stress produced a small but significant 22 percent increase in pHVA and only a nonsignificant 7 percent increase in whole brain HVA (Table 3).

Table 1

The Response of Plasma and Whole Brain HVA in the Rat to Brief Ether Stress vs. Immediate Decapitation ($N = 7$ per Group)

Treatment	Plasma HVA (ng/cc ± SEM)	Whole Brain HVA (ng/g ± SEM)
Brief ether stress	3.1 ± 0.3	83.0 ± 5.8
Decapitation	3.1 ± 0.3	90.5 ± 7.2
t-test	0.13	0.80
p	NS	NS

Table 2

The Response of Plasma and Whole Brain HVA in the Rat to Acute Restraint Stress (90 min) vs. Control ($N = 8$ per Group)

Treatment	Plasma HVA (ng/cc ± SEM)	Whole Brain HVA (ng/g ± SEM)
Control	3.9 ± 0.4	83.3 ± 16.3
Acute restraint stress	4.4 ± 0.3	79.3 ± 16.1
t-test	1.08	0.17
p	NS	NS

Table 3

The Response of Plasma and Whole Brain HVA in the Rat to Chronic Restraint Stress ($N = 6$ per Group)

Treatment	Plasma HVA (ng/cc ± SEM)	Whole Brain HVA (ng/g ± SEM)
Control	2.9 ± 0.1	120.9 ± 3.7
Chronic restraint stress	3.6 ± 0.2	129.0 ± 3.8
t-test	2.88	1.57
p	<.05	NS

Table 4

The Response of Plasma and Whole Brain HVA in the Rat to Varying Doses of Probenecid ($N = 6$ per Group)

Treatment	Plasma HVA (ng/cc ± SEM)	Whole Brain HVA (ng/cc ± SEM)
Vehicle	3.5 ± 0.2	79.5 ± 4.4
Probenecid 20 mg/kg	3.2 ± 0.2	78.6 ± 5.5
Percent change	−8.6	−1.1
Probenecid 40 mg/kg	3.6 ± 0.3	84.8 ± 5.1
Percent change	+2.9	+6.7
Probenecid 60 mg/kg	4.4 ± 0.1[a]	109.8 ± 6.2[a]
Percent change	+25.7	+38.1
Probenecid 80 mg/kg	5.9 ± 0.4[a]	127.1 ± 11.4[a]
Percent change	+68.6	+59.9

[a]Significant at .01 level (two-tailed), by *t*-test, vs. vehicle.

Table 5

Plasma and CSF HVA in Humans With and Without Probenecid Treatment ($N = 7$ per Group)

Treatment	Plasma HVA (ng/cc ± SEM)	CSF HVA (ng/cc ± SEM)
None	15.7 ± 1.4	67.7 ± 4.0
Probenecid	53.3 ± 5.1	249.5 ± 32.5
Percent increase	239.5	268.5
t-test (paired)	9.43	6.19
p	<.001	<.001

In the rat, neither 20 nor 40 mg/kg of probenecid produced a significant alteration in the concentrations of HVA in plasma or brain (Table 4). However, both 60 and 80 mg/kg produced significant and parallel increases in plasma and whole brain HVA (Table 4, Figure 1). The correlation of plasma and whole brain in this experiment was +.078 ($N = 30$) ($p < 0.001$). In psychiatric patients, probenecid (100 mg/kg over 24 hours) produced a highly significant increase in plasma and CSF HVA of approximately equal magnitude (Table 5, Figure 2). The correlation of plasma and CSF HVA in these patients was +0.86.

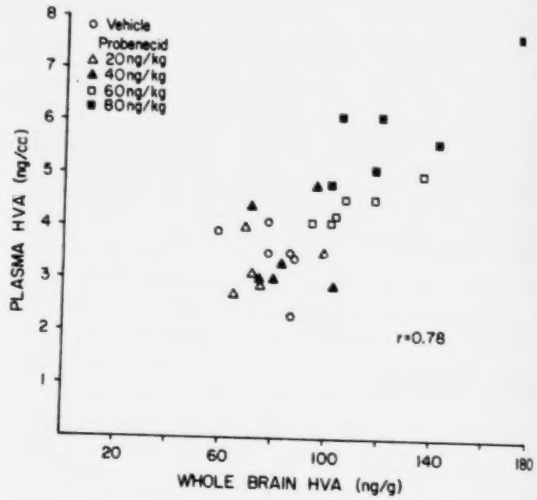

FIGURE 1

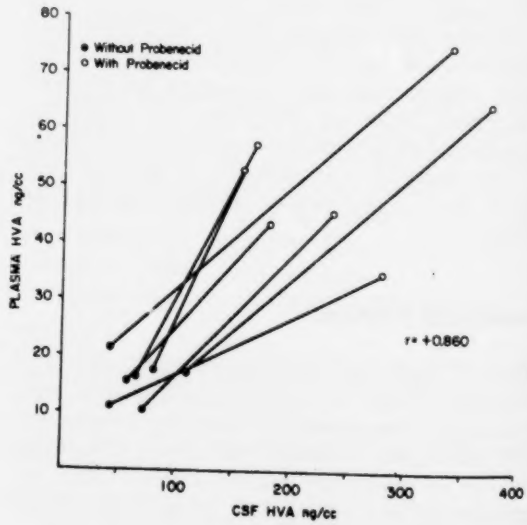

FIGURE 2

Discussion

Acute ether and immobilization stress produced no significant increase in pHVA concentrations in the rat. However, chronic restraint stress, which has been shown to increase levels of catecholamine synthetic enzymes (Kvetnansky 1980), produced a small but significant increase in pHVA. Although these results suggest that chronic, but not acute, stress may selectively increase peripheral production of HVA, two methodologic issues remain to be addressed. First, since even immediate decapitation produces a significant elevation in plasma levels of catecholamines, this method of sacrifice may not produce true "controls" for the examination of the effects of stress on pHVA. The investigators are currently using animals with chronic indwelling arterial cannula for "controls" in studies of the effects of stress on pHVA. Second, chronic stress could elevate pHVA concentrations in ways other than increasing peripheral HVA production. Hemoconcentration and decreased HVA clearance caused by the prolonged struggling and physical exhaustion may be the mechanism for the elevation of pHVA by chronic stress. The investigators are conducting experiments to examine this possibility. Despite these methodologic difficulties, these results suggest that compared to the effects of neuroleptic drugs (Kendler et al. 1981), stress probably has a relatively small effect on pHVA concentrations.

After probenecid administration in both rat and man, plasma concentrations correlate highly with central levels of HVA. In the rat, the threshold dose of probenecid necessary to produce a significant increase in plasma and brain concentrations of HVA was the same (60 mg/kg). These results suggest that selective inhibition of renal excretion of HVA by probenecid without altering transport of HVA from brain may be difficult to achieve. However, since after probenecid, pHVA correlates highly with central measures of HVA, measurement of pHVA levels in man after probenecid may be a useful measure of brain DA turnover.

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Plasma Haloperidol Levels and Clinical Response in Acute Schizophrenia

Irl Extein, M.D.,[1] K.A. Augusthy, M.D.,[1] Mark S. Gold, M.D.,[2] A.L.C. Pottash, M.D.,[2] David Martin, B.S.,[2] and William Z. Potter M.D., Ph.D.[3]

Over the past three decades, neuroleptic medications have become the treatment of choice for schizophrenia, particularly for acute (Casey et al. 1960; Extein 1980) and prophylactic (Davis 1975) treatment of psychosis. However, a significant proportion of schizophrenic patients have an inadequate antipsychotic response to neuroleptics (Ayd 1975). One source of the variability in clinical antipsychotic response may be variability in plasma levels of medication. Several investigators have studied the relationship of neuroleptic levels and response to treatment (Calil et al. 1979; Forsman & Ohmen 1976; Magliozzi et al. 1981; Smith et al. 1979; Tune et al. 1980). Some of these investigators have suggested "therapeutic windows" for plasma levels of neuroleptics, including haloperidol (Forsman & Ohmen 1976; Magliozzi et al. 1981; Tune et al. 1980).

Haloperidol is a potent neuroleptic with a relatively low profile of sedation and cardiovascular effects that is extremely useful in the treatment of acute psychosis (Extein 1980). Steady-state plasma levels are achieved in about 6 days (Forsman & Ohmen 1976). Because haloperidol has no significant active metabolites, it is an ideal medication to use to study the relationship between clinical efficacy and neuroleptic levels. Most other neuroleptics have active metabolites, and studies of plasma levels and clinical response to these medications must involve assays of multiple compounds or dopamine-receptor binding assays (Calil et al. 1979). Magliozzi et al. (1981) have recently reported a therapeutic window for haloperidol levels in schizophrenic outpatients. In order to study the relationship of clinical responses and haloperidol levels in acute treatment, we measured steady-state plasma haloperidol levels and rated clinical response in 18 newly admitted, acutely psychotic schizophrenic inpatients.

[1]Fair Oaks Hospital, Summit, NJ 07901.
[2]Psychiatric Diagnostic Laboratories of America, Summit NJ 07901.
[3]Clinical Psychobiology Branch, National Institute of Mental Health, Bethesda, MD 20205.

Method

Eighteen actively psychotic patients newly admitted to the Fair Oaks Hospital Neuropsychiatric Evaluation Unit and diagnosed by Research Diagnostic Criteria (Spitzer et al. 1978) were included in this study. Fourteen had schizophrenia, undifferentiated or paranoid subtype, and four had schizoaffective disorder. All were treated with haloperidol. Mean age of these patients ± s.e.m. was 26 ± 1 years. The Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham 1962) was done by a research psychiatrist at the time of admission and at regular intervals thereafter. Haloperidol dosage was adjusted by the treating psychiatrist based on standard clinical criteria. Dosage ranged from 7-60 mg daily. Anticholinergic medications were used as needed for extrapyramidal symptoms (EPS). Some patients received some of their haloperidol by intramuscular injection during the first week, but thereafter the medication was administered orally. Blood samples for assay of steady-state plasma haloperidol levels were obtained by venipuncture at regular intervals while patients were receiving haloperidol. Steady-state levels (Forsman & Ohmen 1976), were defined as those obtained at 8 a.m. in the morning 10 hours after the previous dosage of haloperidol in a patient who had been on the same dosage for at least 1 week. Plasma haloperidol levels were determined by gas-liquid chromatography (GLC) with nitrogen-phosphorus selective detection using a modification of the method of Bianchetti and Morselli (1978). The absolute sensitivity of the method was 1 ng/ml with a mean day-to-day coefficient of variation of less than 10 percent. Haloperidol responders were defined as patients showing a decrease of 10 points or more on the BPRS at a given time point. Data are expressed as mean ± s.e.m.

Results

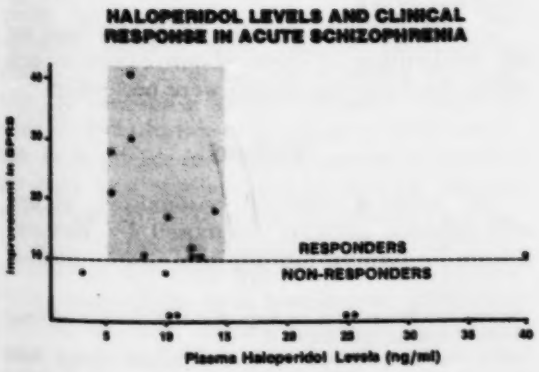
The mean BPRS score on admission was 60 ± 2. Nine patients were responders to haloperidol at the end of 4 weeks. Mean decrease

in BPRS at 4 weeks in these nine patients was 17 ± 3. Of these nine responders, seven had steady-state haloperidol in the therapeutic range suggested by the literature (Forsman & Ohmen 1976; Magliozzi et al. 1981) of 5-15 ng/ml, and two had higher levels. Mean plasma level in the nine patients identified as responders at 4 weeks was 15.6 ± 4.0 ng/ml. Dosage in these nine patients ranged from 10-60 mg daily, with a mean of 27 ± 5 mg daily. Three responders were dropped from the study before 4 weeks, because of severe extrapyramidal syndrome (EPS). All three of these responders had haloperidol levels in the 5-15 ng/ml range. Six patients were nonresponders. Four of these six were dropped from the study before 4 weeks because of poor response Three of these six nonresponders had haloperidol levels outside the 5-15 ng/ml range — two higher and one lower. Mean plasma level in the six nonresponders was 14.4 ± 4.1 ng/ml. Dosage in these six patients ranged from 7-60 mg daily, with a mean of 25 ± 9 mg daily. In summary, 10 of 12 responders but only 3 of 6 nonresponders had haloperidol levels in the 5-15 ng/ml range (*see* Table and Figure).

Table

Plasma Haloperidol Levels and Clinical Response in Acute Schizophrenia

	Plasma Haloperidol Levels	
	5-15 ng/ml	>15 <5 ng/ml
Responders	10	2
Nonresponders	3	3



FIGURE

There was a significant positive correlation between steady-state plasma haloperidol levels and dosage ($r = .68$, $p < .01$). There was no significant correlation between haloperidol levels and change in BPRS.

Discussion

These results suggest that a high proportion of acutely psychotic schizophrenic inpatients who respond to treatment with haloperidol do so at plasma levels in the range of 5-15 ng/ml. This is in basic agreement with a previous study showing outpatients to respond within this approximate range (Magliozzi et al. 1981). There are certain methodological limitations inherent in attempting to define a therapeutic window of plasma levels in an open clinical trial of a therapeutic agent. Dosage adjustments are partially dependent on clinical response, unlike a fixed-dose trial. Also, it is not certain that patients who respond within a given range of plasma levels would not respond at levels above or below this range. Nor is it certain that nonresponding patients would not respond at higher or lower levels. However, this study does identify a range of plasma levels within which most acute schizophrenic patients who respond to haloperidol will fall. There is certainly no linear relationship between haloperidol levels and clinical response. The results here are consistent with either a "therapeutic window" or a "threshold" for effective plasma levels of haloperidol in acute schizophrenia. Individual patient data suggest that nonresponders continue not to respond when haloperidol levels are increased above 15 ng/ml. For example, a 33-year-old woman was unimproved after 2 weeks on haloperidol 15-20 mg daily with plasma levels of 6.7-12.2 ng/ml. She showed no improvement when her haloperidol was raised to 60 mg daily with a plasma level of 25.0 ng/ml.

There are certain practical advantages to measuring plasma haloperidol levels. First, because haloperidol has no known significant active metabolites (Magliozzi et al. 1981), assay of haloperidol alone measures the pharmacologically active compound. Second, the GLC assay (Bianchetti & Morselli 1978) is adaptable to a large volume of clinical samples.

The results presented here, along with previous results from other investigations, suggest that

measurement of plasma haloperidol levels may provide useful guidelines for adjusting medication dosage in schizophrenic patients. Most of the acutely psychotic schizophrenic patients reported here responded with plasma levels in the range of 5-15 ng/ml. Further research needs to be focused on better defining a possible "therapeutic window" or "threshold" for effective haloperidol levels in schizophrenic patients.

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Abnormal Immune Regulation in Schizophrenic Patients

Lynn E. DeLisi, M.D.,[1] and Richard Jed Wyatt, M.D.[2]

Introduction

Associations between psychological states, disease susceptibility and immunity are well known (Stein et al. 1981). In addition, several published reports suggest that schizophrenic patients may have abnormal immune responsiveness and laboratory signs of altered immunity (reviewed by Wyatt et al. 1982) Lymphocyte populations from schizophrenic patients have been shown to contain histologically and functionally abnormal cells as well as abnormal proportions of lymphocyte subtypes (Fessel & Hirata-Hibi 1967, Hirata-Hibi et al. 1982; Kamp 1962; Vartanian et al. 1978). Alterations in plasma and cerebral spinal fluid (CSF) gamma globulin concentrations have also been found (Bock et al. 1970; Domino et al. 1975; Solomon et al. 1969; Strahelivitz et al. 1976; Torrey et al. 1978), as well as evidence of increased antinuclear antibody titres (Gallien et al. 1975; Johnson & Whaley 1975; Zarrabi et al. 1979). Furthermore, the incidence of various diseases known to be associated with immune abnormalities such as rheumatoid arthritis, cancer, asthma, and allergic reactions have been reported to be lower in schizophrenic patients compared with general populations (Baldwin 1979).

In a further attempt to examine this issue and the relationship of these abnormalities to each other, the following studies were performed.

Method

The subjects were all hospitalized, chronic schizophrenic patients diagnosed by Research Diagnostic Criteria (Spitzer et al. 1977), who had

[1]Section on Clinical Pharmacology, National Institute on Mental Health, Bethesda, MD 20205.
[2]Adult Psychiatry Branch, Division of Special Mental Health Research, Intramural Research Program, National Institute of Mental Health, Saint Elizabeths Hospital, Washington, D.C. 20032.

little or no response to conventional treatment, and were residing on the research units of the National Institute of Mental Health, Saint Elizabeths Hospital, Washington, D.C.

Thirty-eight patients (mean age ± S.D. 35.0 ± 10.5) had blood drawn into heparinized plastic syringes on serial occasions for determination of the proportion of lymphocyte subpopulations (*see* Thaler et al. 1977, for review of the immune system). Seven patients were free of medication for at least 1 month; the remaining 31 were medicated on stabilized doses of neuroleptic medication. Forty-seven healthy volunteers (mean age ± S.D. 27.7 + 6.7) from nearby universities and the research laboratory served as controls. Monoclonal antibodies specific to antigens on the surface of T lymphocytes (Leu-1), B lymphocytes (HLA-DR), Suppressor T cells (Leu-2), and Helper T cells (Leu-3) and tagged with fluorescence (Becton-Dickinson Monoclonal Antibody source book), were employed in the following procedure: Lymphocytes were separated from whole blood by the method of Boyum (1968) on a ficoll gradient and centrifuged at 400 g for 50 minutes. The lymphocyte containing band was removed, washed with a buffer consisting of balanced salt solution (Hank's), 2 percent Bovine Serum Albumin (BSA), and .2 percent NaN_3 and spun at 200 g for 10 minutes, then resuspended in 10 ml of buffer and counted in a coulter counter. Cells were then resuspended at a concentration of 1×10^7 cells per cc. Five μl of either Leu-1, Leu-2, Leu-3, or HLA-DR (Becton-Dickinson) was added to 100 μl of cells and vortexed. The suspensions were incubated in the dark on ice for 45 minutes, then pelleted by spinning in an Eppendorf Centrifuge for 15 minutes. The supernatant was aspirated, washed once, and the pellet resuspended in 100 μl of the above buffer. Samples were run through a Becton-Dickinson FACS III using the 488 nM line of an argon laser for excitation. Each sample run (approximately 12 samples per day) was standardized to known chicken erythrocyte light scatter and fluorescence curves. The fluid stream was adjusted to a flow rate of approximately 200 cells per second. The percent fluroescence of the total lymphocyte population (percent of cells having receptors for each monoclonal antibody) was determined on the FACS. Split samples in the same day run had a 2 percent mean variation.

Twenty patients who had HLA-DR binding measured had concurrent plasma immunoglobulins (IgG, IgA, IgM) quantified using an immunofluorescent assay (Clinical Immunology Laboratories, Inc., Los Angeles, Cal.).

Additionally, a total of 51 chronic schizophrenic patients, including 26 of the patients who had lymphocyte subpopulation determinations plus 24 first-episode Diagnostic and Statistical Manual-III (DSM-III) schizophreniform-disordered patients, had serum antinuclear antibody titres determined by an indirect immunofluorescent technique at Clinical Immunology Laboratories. All patients with positive antinuclear antibody titres also had antinative DNA antibody and Histone reactive ANA titres determined (specific tests to diagnose Idiopathic Systemic Lupus Erythematosis and drug-induced Lupus, respectively; Fritzler & Tan 1978).

The schizophreniform patients were sampled prior to neuroleptic treatment over a 2-year period from acute psychiatric admission facilities in the Washington, D.C. area.

Results

Percentages of Leu-1 (total T cells), Leu-2 (Suppressor T cells), Leu-3 (Helper T cells), and HLA-DR (total B cells) are summarized in the Table. The patient group had significantly higher total T cell, as well as B cell, percentages than controls, although an in inverse relationship was suggested for B and T cell percentages for subjects in each group (for patients: Pearson $r = .61$, $p < .003$; for controls: $r = -.51$, $p < .07$). No significant differences were found when comparing the means of the medicated patients with the means of the nonmedicated patients.

B-cell percentages were significantly correlated with IgG plasma concentrations (Pearson $r = .52$, $p = .015$) while not correlated with IgA or IgM concentrations (Pearson $r = .33$; $p = .15$ and $r = -.01$; $p = .97$, respectively). Five of the 20 patients had IgG concentrations higher than the normal range; three of these five had additional elevations in IgA concentrations. One patient had an elevated IgM concentration and normal IgG and IgA, and one patient had an IgG concentration below the normal range. All normal ranges were those established by the Clinical Immunology Laboratories.

Table

Mean (± S.D.) Percent of Total Lymphocytes of Each Lymphocyte Subtype in Schizophrenic Patients vs. Controls

	Percent Leu-1 (Total T's)	Percent Leu-2 (Suppressor T's)	Percent Leu-3 (Helper T's)	Percent HLA-DR (Total B Cells)
Schizophrenic Patients (*N*)	62.4 ± 10.0 (37)	24.1 ± 6.0 (25)	34.7 ± 8.6 (25)	28.0 ± 9.7 (25)
Controls (*N*)	56.7 ± 12.6 (47)	20.9 ± 5.0 (32)	32.9 ± 11.4 (32)	21.3 ± 4.2 (19)
t	2.2	2.2	.68	2.8
p	.03	.03	.50	.008

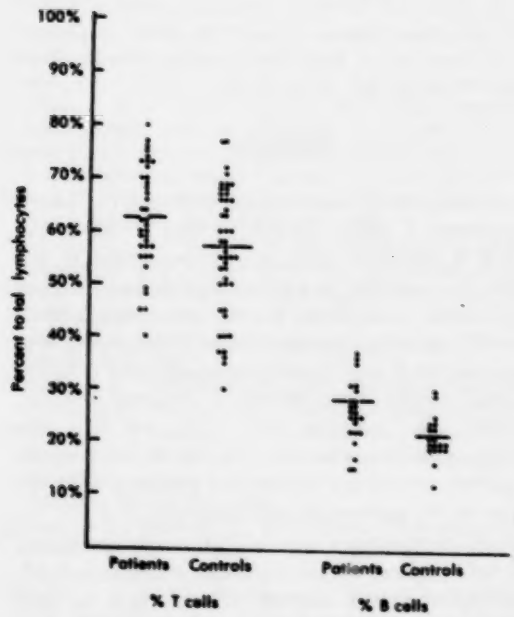

FIGURE 1. Scattergram of the percent HLA-DR binding (B cells) and Leu-1 binding (T-cells) to total lymphocytes in the schizophrenic patients compared with controls.

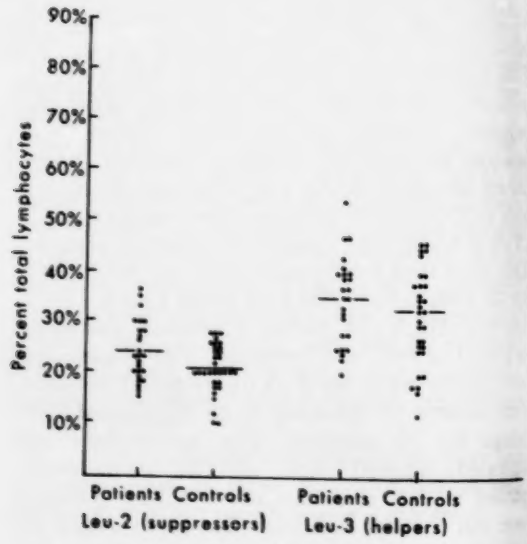

FIGURE 2. Scattergram of the percent Leu-2 (Suppressor T cell) and Leu-3 (Helper T cell) binding to total lymphocytes in the schizophrenic patients compared with controls.

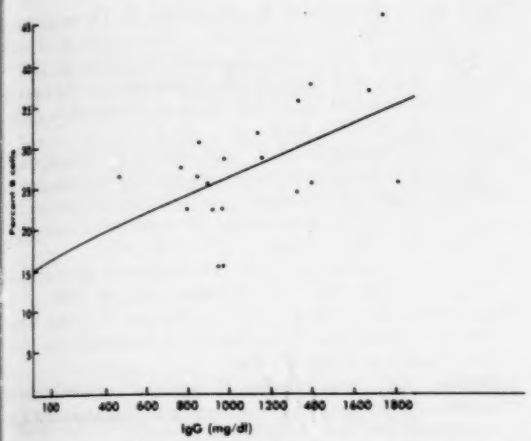

FIGURE 3. IgA concentration vs. percent B cells. Pearson $r = .53$. Mean percent B cells = 27.2 ± 7.2; mean IgG concentration = 1113.7 ± 356.

Antinuclear antibody titres were determined to be positive (> 1/10) of 21.7 percent of the chronic schizophrenic patients and 20.8 percent of the first-episode schizophrenic patients. It is known to be positive in 1-5 percent in the general population (Panush 1979). Positive antinuclear antibody titres did not correlate with elevated immunoglobulin concentrations or elevated proportions of B or T cells. None of the patients with positive antinuclear antibody titres had evidence of either antinative DNA antibodies or anti-Histone reactive DNA antibodies.

Discussion

The data presented here show small differences between schizophrenic and control populations in both the cellular and humoral immune systems. While a generalized decrease in the production of immunoglobulins among chronic schizophrenic patients had been previously found, (DeLisi et al. 1981), a subgroup of patients in the present study had elevated IgG concentrations that were correlated with elevated proportions of the lymphocyte subtype (B cells) that produces them.

These changes may be consistent with the notion that neuroleptic medications alter the immune response. All chronic schizophrenic patients studied had previously been under neuroleptic treatment for several years. That neuroleptics affect the immune system is supported by several lines of evidence. Chlorpromazine has been linked to the presence of abnormal lymphocytes in the blood of schizophrenic patients (Fieve et al. 1966) and the development of systemic lupus erythematosis (Ananth & Minn 1973; Dubois et al. 1972; Fessel & Solomon 1960), an immune complex disorder. Antinuclear antibodies have also been associated with long-term neuroleptic treatment (Gallien 1975; Johnstone & Whaley 1975; Zarrabi et al. 1979). Lovett et al. (1978) have reported a decrease in antibody production *in vitro* by B cells associated with chlorpromazine and Ferguson et al. (1978) reported a suppressive effect of chlorpromazine on several *in vitro* measures of T lymphocyte responsiveness. In addition, *in vivo* proportions of B and T lymphocytes have been shown to return to normal after discontinuation of neuroleptic medication (Ferguson et al. 1978; Liedeman & Prilipko 1978).

The increased proportions of B and T lymphocytes found in our studies, however, may not solely be a result of neuroleptic medication. The few medication-free patients in our studies did not have proportions of B and T cells different from the medicated patients and contrary to the Lovett et al. (1978) study, the increases in B cell percentages were associated with increased antibody production. Furthermore, a recently published report of histological abnormalities in lymphocytes of schizophrenic patients defines distinct abnormalities present in unmedicated chronic schizophrenic patients as well as first-episode acute schizophrenics (Hirata-Hibi et al. 1982).

Heath and Krupp (1966) have hypothesized that abnormal immunity in schizophrenic patients may be the result of an autoimmune disorder and reported the presence of antibrain antibodies in postmortem brain specimens from schizophrenic patients. The present study supports previous findings of a 20-25 percent incidence of positive antinuclear antibody titres that are not specific for lupus erythematosis in chronic schizophrenic patients (Gallien et al. 1975; Johnstone & Whaley 1975; Zarrabi et al. 1979). The increased antinuclear antibody titres in first-episode schizophrenic patients never medicated with neuroleptics, and the negative titres of antibodies characteristic of drug-induced lupus, suggest that this finding in chronic schizophrenic patients is

not simply an effect of long-term medication. Further studies are necessary to determine if an autoimmune phenomena is related to the etiology of schizophrenia.

Torrey et al. (1978) have proposed a viral etiology to schizophrenia subsequent to their findings of specific increases in viral antibody titres. Chronic viral infection, in turn, may cause multiple alterations in immune response. We have not determined in the present studies whether increased viral antibody titres are associated with these abnormalities. Even if found, it would not be clear whether the increased viral antibody titres were associated with the pathology of the illness itself or a consequence of altered immunity.

Finally, the differences reported here are small. It is uncertain if these alterations in immune functioning are related to reported altered incidences of various autoimmune, infectious, and neoplastic disorders in schizophrenic populations.

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Abnormal Scans in Young Schizophrenics

S. Charles Schulz, M.D.,[1] Miriam Koller, M.D.,[1] Pulla R. Kishore, M.D.,[1] Robert M. Hamer, Ph.D.,[1] and Robert O. Friedel, M.D.[1]

Introduction

Although brain abnormalities have been reported for years in the psychiatric literature, the use of the computed tomography (CT) scanner allowed investigators to assess the brain in some new ways. Johnstone et al. (1976) and Weinberger et al. (1979a) reported a difference in ventricular size between schizophrenic patients and control subjects. Since these reports have been published, a significant amount of research has appeared which has bolstered their significance. Correlations of neuropsychological tests such as the Halstead-Reitan Battery (Donnelly et al. 1980) and Luria-Nebraska Test (Golden et al. 1980) and CT scale abnormalities have been demonstrated. In addition, enlarged lateral ventricles in schizophrenic patients has been associated with poor response to antipsychotic agents when compared to schizophrenic patients with normal-sized ventricles (Weinberger et al. 1980). Increased sulcal size of the cerebral cortex (Weinberger et al. 1979b) and atrophy of the cerebellar vermis (Weinberger et al. 1979c) have also been noted.

[1]Medical College of Virginia, Richmond, VA 23298.

In studies reported to date, the patients have usually been ill and have received treatment for some time. The investigators of the early reports hypothesized that the CT scan changes would probably be present early in the course of the illness because there was no correlation with increased ventricular brain ratio (VBR) or lenth of time since onset of symptoms (Weinberger et al. 1979a). The purpose of this investigation was to examine the CT scans of young schizophrenics, many of whom had not received neuroleptics.

Methods

The patients studied included all consecutive admissions diagnosed as schizophrenic (or schizophreniform) who were 22 years old or younger and had not been ill or treated with medication for more than 24 months. They included 10 males and 5 females (total $N = 15$) with average age of 17.1 years (range 15 to 22). They had been ill 13.7 ($\pm$ 2.1 S.E.) months and treated for an average of 5.2 months. Ten had never received neuroleptics. No patients had significant medical illness or mental retardation.

The control group were selected at random by the neuroradiologist from CT scans read as normal. There average age was 16 (13 to 19).

The ventricular brain ratio (VBR) was obtained by planimetric measurement performed as described by Weinberger et al. (1979a). Results were analyzed by application to *t*-test after log transformation of the VBR measures to equalize the variances.

Results

The schizophrenic patients had a mean VBR of 8.3 $\pm$ 4.9 S.D. which was significantly larger than the control population whose mean VBR was 2.7 $\pm$ 2.35 S.D. ($p < .0001$).(Figure 1)

There was no correlation with the length of time since the onset of symptoms and VBR. (Figure 2)

When a standard of "normality" was constructed by adding two standard deviations to the mean of the control group, it was noted that 8/15 (53%) patients had "abnormal" VBRs. Even when compared to adult standards of abnormality (VBR > 10), 7/15 were judged to be large.

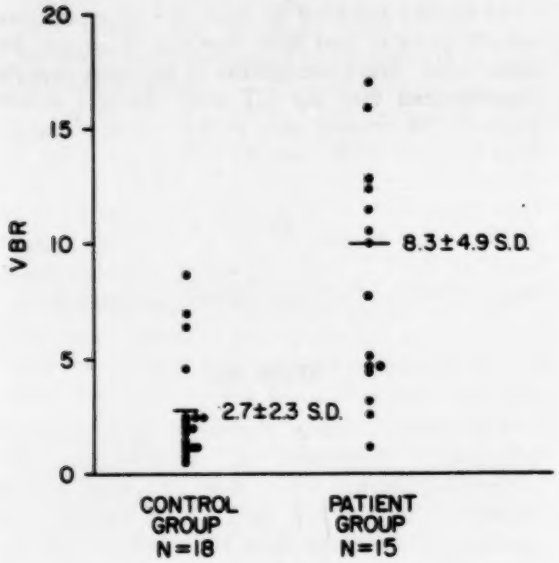

FIGURE 1.

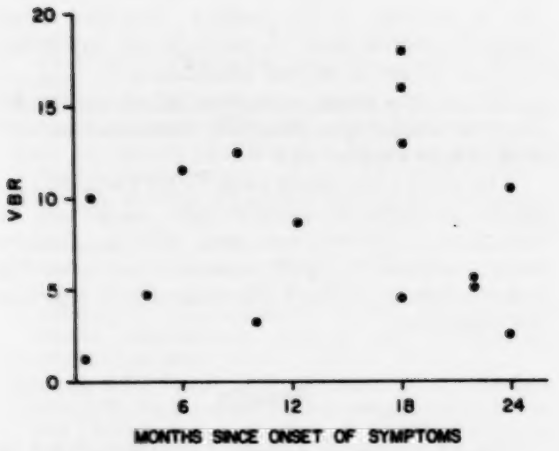

FIGURE 2.

Of the three schizophreniform patients in the study, one had an abnormal scan (VBR = 10). No tumors were seen in this series.

Conclusion

These results corroborate the finding of increased VBR in schizophrenic patients and are comparable in magnitude to Weinberger's initial report. This finding is consistent with the hypothesis that the CT scan abnormality is present early in the illness and is not a result of treatment with medication or institutionalization.

Although the prevalance of the increased VBR was about 50 percent in the authors' group of patients, this may not be an accurate assessment of the rate of abnormality in all young schizophrenics, as the Medical College of Virginia is a tertiary referral center.

There are other parameters concerning these patients that are currently being evaluated.

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Computer EEG Drug Data Base in Psychopharmacology and in Drug Development

Turan M. Itil, M.D.,[1] Gopi N. Menon, M.D.,[2] and Kurt Z. Itil, B.A.[3]

The quantification of human electroencephalogram (EEG) with a digital computer, called computer-analyzed EEG (CEEG™) (Itil 1974), is the only objective method in the development of new psychotropic drugs in humans. The method was developed based on a series of observations and hypotheses.

One of these observations has been that all drugs that are effective on human behavior (psychotropic drugs) also produce changes in human brain function, which can be established by scalp recorded EEG. Some of the psychotropic drug-induced changes in EEG are relatively minimal and therefore difficult to evaluate visually. Thus, it is imperative that the EEG be quantified. The most advanced quantifications of EEG are via specific-purpose computers. Although it is recorded with similar equipment, and the recorded activities on paper are the same, the computer-analyzed EEG for psychotropic drug development is distinctly different from neurologically used "conventional" EEGs for clinical diagnosis. Whereas a "conventional" EEG is primarily concerned with very slow waves (less than 7 cps) and "abnormal" waveforms such as sharp waves, spikes, spikes and waves, focal abnormalities, and paroxysmal activities, the CEEG™ for psychopharmacology is primarily concerned with "normal" waveforms, and normal frequency (alpha, beta, and faster activities) and amplitude distributions. Only 3 of the 22 measurements of a CEEG™ (period analysis) are used in a conventional "clinical" EEG. The remainder of the 19 measurements are not considered in the conventional electroencephalography for the purpose of clinical diagnosis, although they are important in psychopharmacology. Therefore, in order to differentiate from the conventional EEG, the computer-analyzed EEG was termed "computer-analyzed bio-electrical potentials" (CABP) or "computerized EEG" (CEEG™) by Itil (1974) or cerebral electrometry by Fink (1974).

CEEG™ is most successfully applied during Phase I "safety" clinical pharmacology trials and Phase II psychotropic drug studies using the methods of quantitative pharmaco-EEG (QPEEG™) (Itil 1974; Itil et al. 1971). QPEEG™ is the method involving the use of digital computer-analyzed EEG and a series of statistical procedures for the establishment of the mode of action of a new compound in humans after an orally administered single dose. More specifically, this method can help to:

A. Determine the potency (quantity) of *central nervous system (CNS)* effects;

B. Estimate the *onset and duration* of the CNS effects;

C. Predict clinical usefulness *(psychotropic properties)* of new drugs.

Until recently, the CEEG™ drug classification system was subjective. Classification was made based on "visual inspection" of CEEG™ profiles of a compound. More recently, the technique has become automated and objective. In the past ten years, the CEEG™ profiles of a variety of marketed psychotropic drugs were obtained in standard trials using the QPEEG™ method. These data have recently been reanalyzed using both period analysis and EEG power spectral density analysis programs, and stored in a data base format in a minicomputer. The HZI Research Center computer data base includes the CEEG™ effects of 105 clinically well-known psychotropic compounds in 810 male and female volunteer subjects in the age range of 21 to 35, collected in 92 QPEEG™ studies. When a new drug is studied, first its CEEG™ profile is obtained based on a QPEEG™ trial. Subsequently, the CEEG™ profiles of this compound are compared with the CEEG™ profiles of data base psychotropic drugs using correlation statistics to classify the new drug.

Replicability, reliability, and validity of the HZI computer data base to classify psychotropic drugs were tested in a series of studies (Itil et al. 1981). It was established that the computer data

[1]Division of Biological Psychiatry, New York Medical College, Valhalla, NY 10591.
[2]HZI-Europe, Amsterdam, The Netherlands.
[3]HZI Research Center, Tarrytown, NY 10591.

base is able to classify the marketed anxiolytics, psychostimulants, and antidepressants statistically significantly better than chance ($p < .00001$ for anxiolytics, $p < .00001$ for psychostimulants, and $p < .0001$ for antidepressants; binomial statistics). Classification of marketed neuroleptics was not better than chance, in part because the doses of neuroleptics administered in these studies were less than those used for therapeutic purposes in clinical practice.

Investigations in recent years have demonstrated (Itil et al. 1977, 1979, 1980) that application of the CEEG™ and a computer EEG drug data base are helpful not only in *quantitatively determining* the central nervous system (CNS) effects of drugs as well as the lowest CNS effective dose and *predicting psychotropic properties* of compounds, but also in predicting *psychotropic potency* and the *lowest psychotropic effective single dose* of a new compound using QPEEG™ methodology.

In this paper the use of CEEG™ will be presented in a series of Phase I single-dose tolerance and safety studies.

QPEEG™ Studies

Etizolam*

ETIZOLAM (Y-7131) [6-(o-Chlorophenyl)-8-ethyl-1-methyl-4H-s-triazolo (3,4-c) thierno(2,3-e) (1,4)diazepine] is a new derivative of the thienodiazepines and has biochemical profiles similar to diazepam, but differs from it in exhibiting an inhibitory effect on the NE turnover and its uptake; thus, antidepressant effects of etizolam were also predicted.

A double-blind crossover QPEEG™ study with latin-square design was conducted in 10 healthy male and female volunteers. Etizolam was orally administered in single doses of 0.5 mg, 1 mg, and 2 mg. Control compounds were 5 mg diazepam, and placebo. CEEG™ recordings were done pre, 1,3, and 6 hours after drug. The results were as follows:

1 - CNS effects of all dosages of etizolam and 5 mg diazepam could be discriminated (multivariate randomized T^2) from placebo at the statistical level ($p = .05 - .002$). Therefore, the lowest CNS effective dose of etizolam was established as 0.5 mg. Etizolam also produced statistically signifi cant dose- and time-related CNS effects.

2 - The mode of action of etizolam resembles that of benzodiazepine anxiolytics. The HZI Research Center computer drug data base classified all doses of etizolam as anxiolytic (Figure 1). The similarity coefficient with data base anxiolytics was for 0.5 mg etizolam = .7 (mean), for 1 mg = .79, for 2 mg = .90. The control compound (5 mg diazepam) was also classified as anxiolytic, which indicated that the data collection and analysis systems were accurate and the subjects adequately responded to an anxiolytic. Based on a two-dimensional drug classification system, it was demonstrated that the CNS effects of etizolam, next to anxiolytics, showed greater similarity to tricyclic antidepressants than those of diazepam (similarity coefficient was .82).

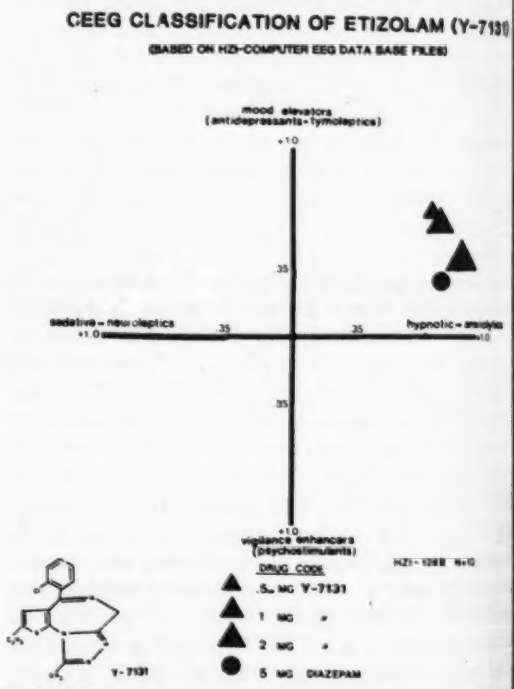

FIGURE 1. According to a two-dimensional classification system (based on the two highest similarity coefficients with computer data base drug groups), all doses of etizolam and diazepam were classified primarily as hypnotic-anxiolytic and secondarily as antidepressant (mood elevator). The highest hypnotic-anxiolytic property was seen with 2 mg etizolam and the lowest with 0.5 mg etizolam; particularly the lower doses showed more mood elevator effects than that of diazepam.

*Yoshitomi Pharmaceutical Industries Ltd., Osaka 540-91, Japan.

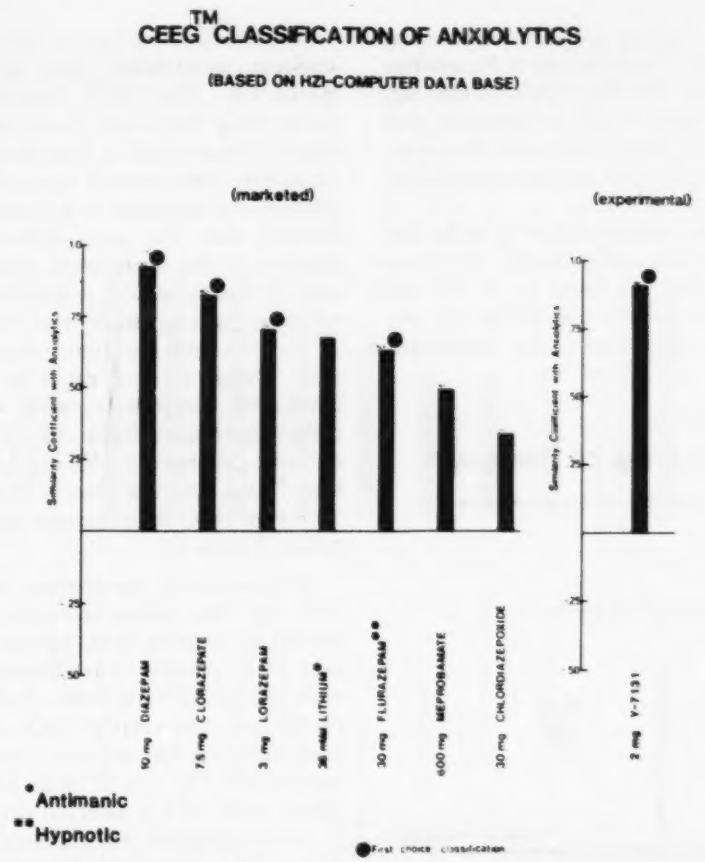

FIGURE 2. Among the marketed anxiolytics, diazepam showed the highest similarity coefficient with data base anxiolytics, and chlordiazepoxide the lowest; etizolam's (2 mg) similarity coefficient was slightly less than that of 10 mg diazepam.

3 - The anxiolytic potency of etizolam with 2 mg was slightly less than 10 mg diazepam but more than 7.5 clorazepate and 3 mg lorazepam (Figure 2).

4 - The minimum psychotropic effective single dose of etizolam probably starts lower than the minimum dose (0.5 mg) administered in this study.

In conclusion, it was established that etizolam is a very potent CNS effective compound with a significant effect on the CNS system at 0.5 mg or even lower. Its mode of action is similar to those of benzodiazepine hypnotic-anxiolytics. Thus, it is predicted to be effective in anxiety patients. The hypnotic-anxiolytic potency of 2 mg etizolam was found to be just slightly less than 10 mg diazepam. In clinical trials, the use of a 0.5 mg single dose is recommended.

Binodaline

BINODALINE (Sgd - Scha 1059)*. (1-[W-dimethylaminoethyl-methyl]-amino-3-phenyl-indole hydrochloride) is a compound with mood elevating properties similar to imipramine but stronger than amitriptyline, dibenzepin, and dimethacrine. It has neither monoamine oxidase-inhibiting properties nor anticholinergic activity. It has been shown to be devoid of serious toxic effects in animal toxicological studies.

*Siegfried AG, Zofingen, Switzerland.

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A double-blind crossover QPEEG™ study was conducted in 10 healthy male subjects. Binodaline was used in four doses 150, 300, 450, and 600 mg. Control compounds were 50 mg imipramine, and placebo. The CEEG™ recordings were done pre, 1,3, and 6 hours after drug or placebo administration. The results were as follows:

1 - The CNS effects of binodaline could be discriminated (multivariate randomized T^2) from placebo in 300 and 600 mg doses ($p = .01$ and .05, respectively). However, binodaline did not produce any appreciable statistically significant dose- and time-related CNS effects.

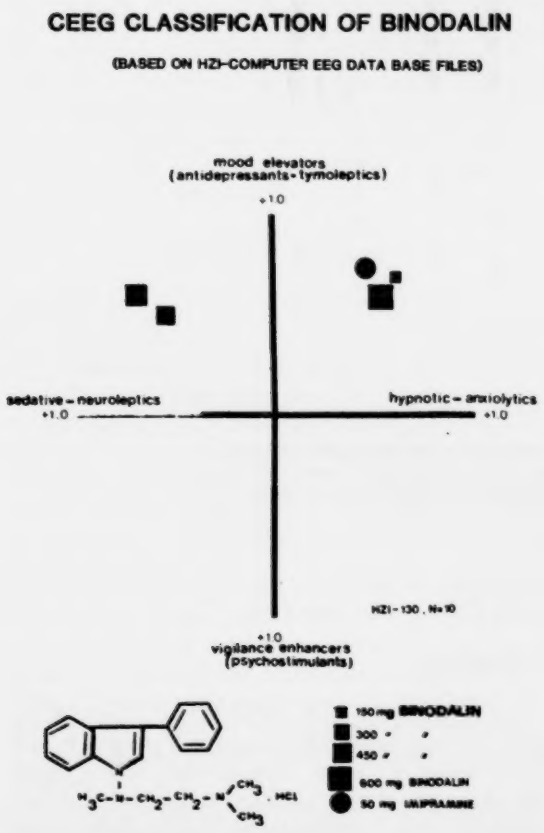

FIGURE 3. Based on the two-dimensional classification system, all dosages of binodaline were classified primarily as mood elevator, whereas 150 and 600 mg also showed hypnotic-anxiolytic properties, and 300 and 450 mg showed secondary sedative-neuroleptic effects. Imipramine was classified primarily as mood elevator and secondarily as hypnotic-anxiolytic.

2 - Mode of action of binodaline in all four dosages resembled that of tricyclic antidepressants. The HZI Research Center computer drug data base classified all dosages as a mood elevator with a first choice (Figure 3). Imipramine, the control compound, was, as expected, also classified as a mood elevator. This indicated that the data collection and analysis systems of the study were reliable, subjects adequately and accurately responded to a known mood elevator, and the study was therefore valid.

3 - The mood elevator potencies of binodaline were similar to each other in all dosages tested (similarity coefficient with data base mood elevators ranged from .64 to .77). The mood elevator potency of 150 mg binodaline was less than 75 mg amitriptyline or 75 mg imipramine or 30 mg mianserin, but more than 75 mg nortriptyline (Figure 4).

In conclusion, binodaline, in doses as low as 150 mg, has mood elevator-like CNS effects similar to tricyclic mood elevators. Its discrimination from placebo was, however, possible only with 300 and 600 mg doses. It did not produce any significant dose-related CNS effects. These suggest that binodaline may have high biological variability. Thus, it is likely to have therapeutic effects primarily in selected depressed patients.

Oxiracetam*

OXIRACETAM (ISF-2522)(4-hydroxy-2-oxo-1-pyrrolidinacestamide) is a gaba-gabol derivative similar to piracetam, and was found to be active on both some behavioral tests and brain biochemical parameters indicative for improvement of learning and memory (Pifferi et al. 1976). Based on animal toxicological data, it was predicted that oxiracetam can be administered in humans up to 2400 mg single dose without any serious side effects.

A single rising dose tolerance and efficacy study was conducted with oxiracetam in seven healthy subjects using a QPEEG™ study design. Five dosages of oxiracetam (200, 400, 800, 1200, and 2400 mg) were administered with randomized control compounds (15 mg dextroamphetamine, 1200 mg piracetam, placebo). The results were as follows:

*ISF S.p.A.-Milano, Italy.

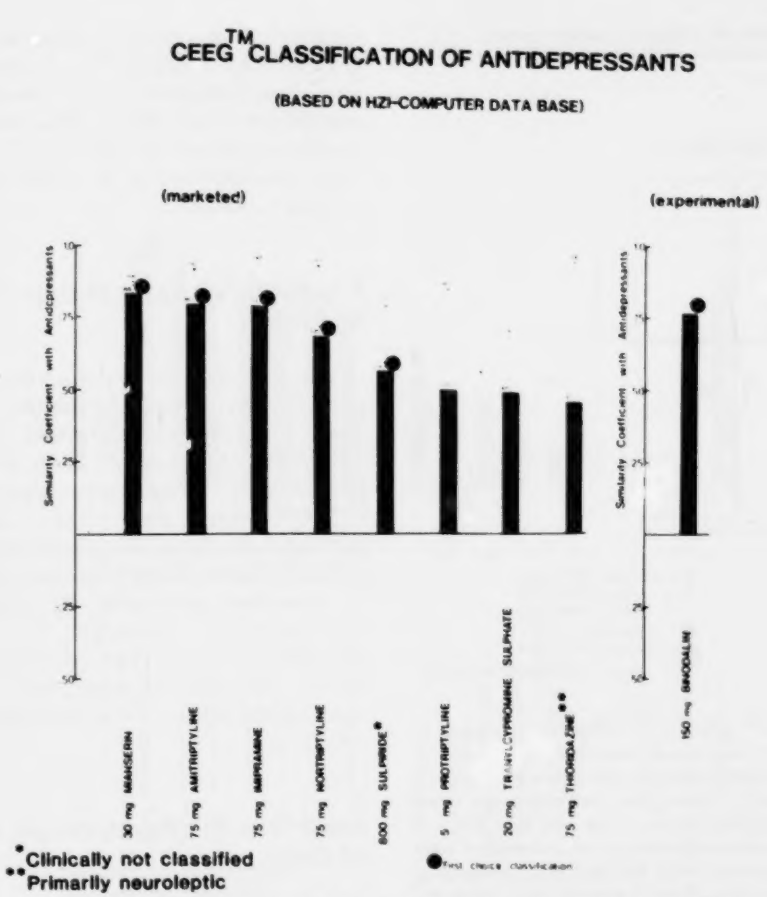

FIGURE 4. Among the marketed mood elevators, mianserin showed the highest, and thioridazine the lowest similarity coefficient with data base mood elevators. In this dose the mood-elevating properties of binodaline were less than mianserin (30 mg), amitriptyline (75 mg), and imipramine (75 mg), but more than nortriptyline (75 mg).

1 - The CNS effects of oxiracetam could be discriminated (univariate statistics) from placebo in dosages of 1200 and 2400 mg. Certain CEEG™ measurements indicated dose and time-related CNS effects of oxiracetam (regression analysis).

2 - The mode of action of oxiracetam on brain function is similar to that of vigilance-enhancing ("psychostimulant") compounds. The HZI Research Center computer drug data base classified oxiracetam in doses of 1200 mg (third choice) and 2400 mg (first choice) as a vigilance enhancing compound similar to 1200 mg piracetam and 15 mg dextroamphetamine (Figure 5).

3 - Based on the comparison of the similarity coefficients of oxiracetam with those of marketed vigilance enhancing compounds, it was predicted that 2400 mg oxiracetam would have vigilance enhancing effects which are less than 20 mg dextroamphetamine but more than 200 mg caffeine or 1200 mg piracetam (Figure 6).

4 - The lowest clinically therapeutic single dose of oxiracetam, which is safe and CNS effective, was predicted to be 1200 mg.

A double-blind clinical trial confirmed the CEEG™ prediction. Oxiracetam is effective in the improvement of memory, similar to piracetam, in daily doses of 2400 mg (Itil et al. in press).

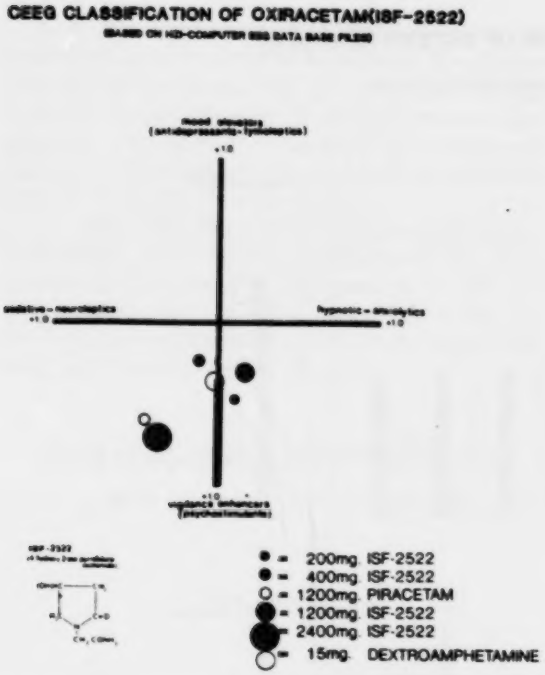

FIGURE 5. CEEG™ profiles of different dosages of ISF-2522 and control compounds were classified based on the HZI Research Center computer drug data base using a two-dimensional model. Correlation coefficients are based on the four recording conditions (1 hr and 3 hr RR and RT recordings), Dextroamphetamine was classified only as a vigilance enhancer, with no positive correlations with other drug groups. Four hundred and 2400 mg ISF-2522 and piracetam were classified between vigilance enhancers and sedative-neuroleptics, whereas 200 mg ISF-2522 and 1200 mg ISF-2522 were classified between vigilance enhancers and hypnotic-anxiolytics.

Conclusion

The use of CEEG™ in early drug screening (Phase 1) in man using QPEEG™ methodology and a computer EEG data base of established drugs is useful for the following:

Establishment of CNS Efficacy of Drugs

All clinically useful psychotropic drugs possess significant effects on human brain function, as established by computer analyzed scalp record human EEG (CEEG™). Accordingly, to be useful psychotropic, a new compound must ha significant CNS effects. This can be determine by discrimination of the CEEG™ effects of a dr from placebo, and by establishing dose and ti related CNS effects.

Prediction of Psychotropic Properties of Drugs

The HZI Research Center drug data base ca predict psychotropic properties of drugs aft single oral dose administration. The validity an reliability of the HZI data base to classif psychotropic drugs was successfully tested CEEG™ drug data base classification o psychotropic properties can be independent of th animal pharmacology and biochemical propertie or chemical structures of drugs. This wa demonstrated through the discovery o psychotropic properties of drugs via CEEG which did not possess the "typical" pha macological action of marketed psychotropics (Ha 1981).

Prediction of "Psychotropic Potency" of Drugs

It was established that the clinically most pote drugs also produce the most "typical" CEEG profiles, which show the highest similarity coeffi cient with the data base drugs.

Prediction of "Psychotropic Effective" Dose

The classification of the CEEG™ profiles of dif ferent doses of well-known drugs demonstrate that the minimum single dose, tolerable in man and can be discriminated from placebo, and i classified by the HZI data base as psychotropic, i also similar to the clinically therapeutically effec tive single three times a day (t.i.d.) or four times a day (q.i.d.) dose (Figure 7).

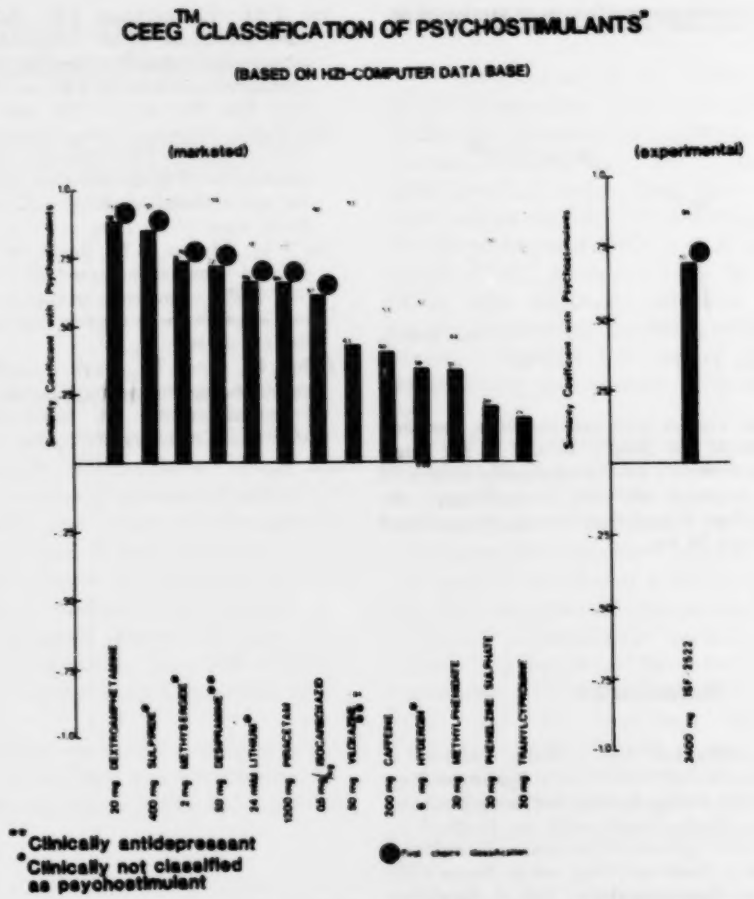

FIGURE 6. Of the marketed compounds which have some vigilance-enhancing properties, dextroamphetamine showed the highest, and tranylcypromine the lowest similarity coefficient with data base vigilance enhancers. Oxiracetam (2400) mg) has less vigilance-enhancing properties than 20 mg dextroamphetamine but more than 200 mg caffeine.

If a drug has significant CNS effects (discrimination from placebo) but cannot be classified by the data base, it is hypothesized that this compound has a different mode of action from existing major psychotropic drug groups (hypnotic-anxiolytics, mood elevators, sedative-neuroleptics, and vigilance enhancers); thus, it will have a new type of psychotropic property. On the other hand, if a drug is classified by the computer data base but cannot be discriminated from placebo, it is assumed either the dose studied is low, or sample size too small, or biological variability of this compound is too high; thus, this compound will not be a broad spectrum, effective psychotropic.

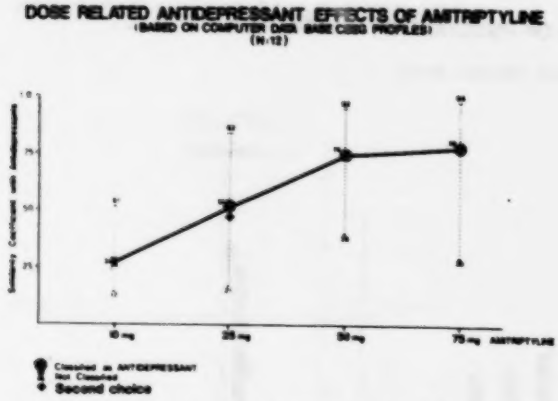

FIGURE 7. In our studies with amitriptyline, the computer data base could not classify 10 and 25 mg single dosages, with a first choice, but could classify 50 and 75 mg dosages as a mood elevator. Accordingly, the therapeutic single dose of amitriptyline can be predicted to be between 25 and 50 mg.

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The First Clinical Study of BW-234U in Schizophrenia

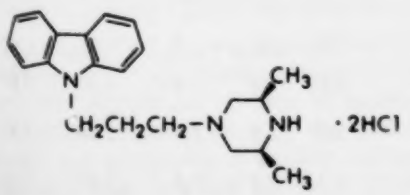
Jonathan Davidson, M.D.,[2] Robert Miller, M.D., Ph.D.,[1,2] Martha Wingfield, M.D.,[1,3] William Zung, M.D.,[2] and Anthony T. Dren, Ph.D.[4]

Introduction

Currently available antipsychotic drugs are associated with a number of unwanted effects, of which extrapyramidal and autonomic changes are particularly troublesome. A new carbazole compound, BW-234U, (Figure 1), promises to have antipsychotic activity without concomitant extrapyramidal or autonomic change. The results of testing BW-234U in animals, and the relevant underlying models, are presented elsewhere (Ferris et al. 1982).

This report describes an interim analysis in the first clinical study of the drug in schizophrenic inpatients; this study was still ongoing at the time of the report.

BW 234U



9-[3-(3,5-Dimethyl-1-piperazinyl)propyl]carbazole dihydrochloride

FIGURE 1

[1]John Umstead Hospital, Butner, NC 27509.
[2]Duke University Medical Center, Department of Psychiatry, Durham, NC 27706.
[3]University of North Carolina, Department of Neurology, Chapel Hill, NC 27514,
[4]Wellcome Research Laboratories, Research Triangle Park, NC 27709.

Method

To be included in the study patients had to fulfill Diagnostic and Statistical Manual-III (DSM-III) criteria for schizophrenia, give informed consent, be between 18 and 55 years of age, be in good physical health, and have clinically acceptable values on SMA12, hematology, urinalysis, electrocardiograph (ECG), and electroencephalograph (EEG). Excluded from the study were patients with medically unstable illness, organic brain syndrome, mental retardation, blood pressure outside the range of 150/90, drug dependency, and women of childbearing potential.

All patients were assigned to receive BW-234U for up to 28 days. When the study was initiated, a starting dose of 100-200 mg/day was used, to be increased up to a maximum of 600 mg/day. This maximum limit was later reduced to 400 mg after one patient developed a seizure. Dosing, which was flexible, was administered on a b.i.d. basis.

Weekly assessments included the Clinical Global Impressions of Severity (CGI-S) and Improvement (CGI-I), Brief Psychiatric Rating Scale (BPRS), Inpatient Multidimensional Psychiatric Scale (IMPS), as well as the Simpson-Angus (SA) and Abnormal Involuntary Movement Scale (AIMS) scales which measured extrapyramidal and other movement disorder.

Results

Twelve patients entered the study, one dropping out within a week for family reasons unrelated to treatment. Eleven patients completed a minimum 3-week treatment and nine completed 4 weeks. One terminated treatment at 3 weeks because of a seizure, and the other recovered and was discharged. Baseline demographic data showed that all patients were male, eight were white and three black, mean age was 27.1 years (range 18 to 42). Ten patients were unmarried and one was separated. Using DSM-III subtypes, six patients had paranoid schizophrenia, four, chronic undifferentiated, and one, disorganized schizophrenia.

Mean doses at each weekly assessment were as follows: 295, 327, 363, and 344 mg/day. The median doses at each time were 300, 300, 400, and 300 mg.

CLINICAL GLOBAL IMPRESSION (CGI) SCALE

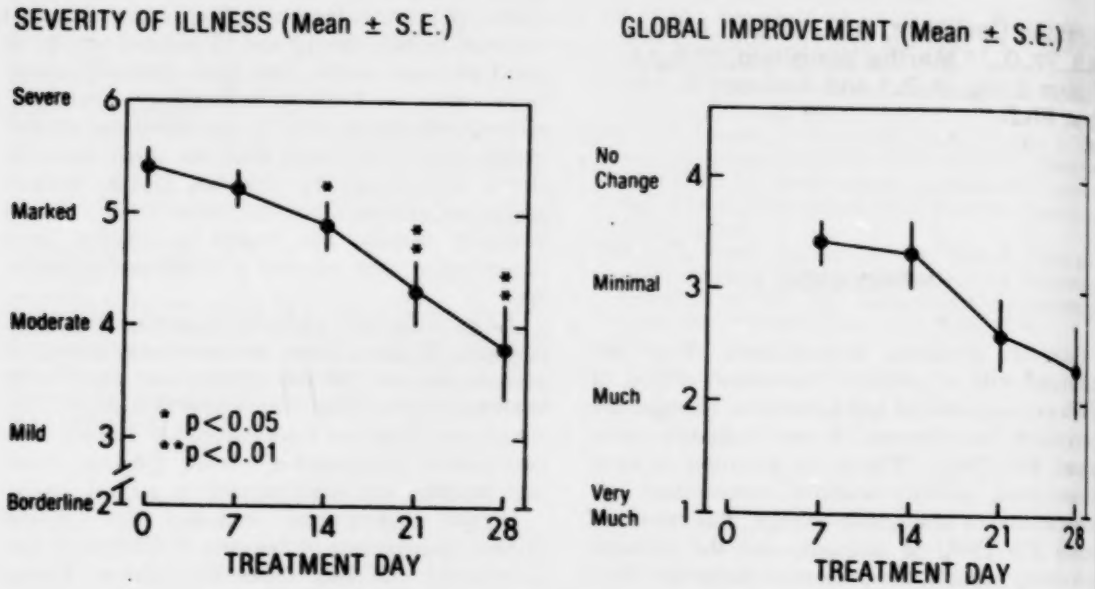
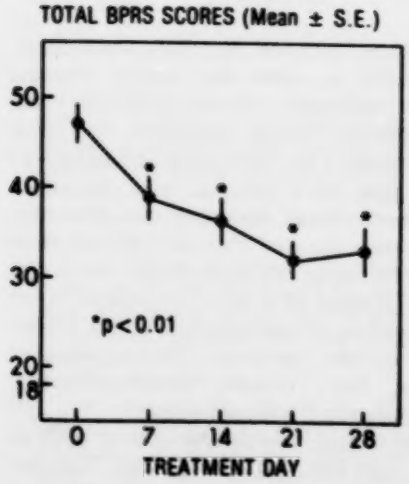


FIGURE 2

BRIEF PSYCHIATRIC RATING SCALE (BPRS)



BPRS FACTOR SCORES (Means)

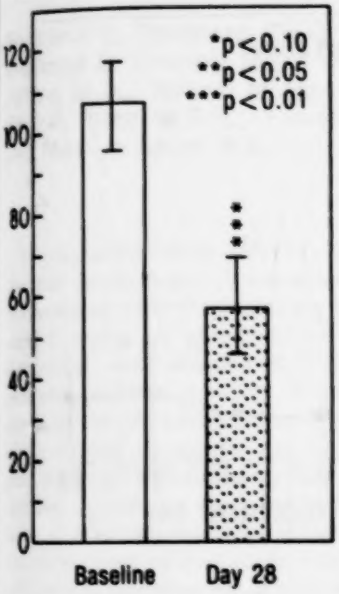
Factor	Bo	1	2	3	4
I. Anxiety/Depression	2.6	1.9*	1.8**	1.6**	1.6**
II. Anergia	3.0	2.6	2.4**	2.0**	2.3*
III. Thought Disturbance	3.1	2.8	2.6	2.3*	2.4*
IV. Activation	1.4	1.4	1.3	1.3	1.2
V. Hostile/Suspiciousness	2.1	1.8	1.8	1.6*	1.6*

*p<0.05; **p<0.01

FIGURE 3

INPATIENT MULTIDIMENSIONAL PSYCHIATRIC SCALE (IMPS)

TOTAL IMPS SCORES (Mean ± S.E.)



IMPS FACTOR SCORES (Means)

Factor	Baseline	Day 28
I. Excitement	4.0	1.0*
II. Hostile/Belligerence	7.1	3.5*
III. Paranoid Projection	6.1	3.5**
IV. Grandiose Expansiveness	2.1	0.6*
V. Perception Distortion	11.7	4.8***
VI. Anxious/Intropunitiveness	16.1	6.5***
VII. Retardation/Apathy	22.7	15.3*
VIII. Disorientation	0.3	0.3
IX. Motor Disturbances	3.6	1.7
X. Conceptual Disorganization	2.8	1.5

FIGURE 4

Efficacy Scales

As shown in Figure 2, Global Severity of Illness decreased at each week from a baseline score of 5.3 to 3.8 by Week 4. This change was statistically significant at Weeks 2, 3, and 4. Overall improvement on the CGI-I was also noted.

The total BPRS score declined from 45.2 before treatment to 33.5 at Week 4 (Figure 3). Improvement was significant relative to baseline at all time points. Examination of the BPRS factors showed that symptoms of anxiety and depression responded first, followed at Week 2 by anergia, and at Week 3 by improvement on thought disorder, hostility, and suspiciousness.

Use of the IMPS (Figure 4) at pretreatment and termination showed a significant improvement on paranoid projection, perceptual distortion, anxious intropunitiveness, and on the total score.

Safety Data

No changes were noted on the SA and AIMS scales (Figure 5), consistent with the original expectation that this drug has few extrapyramidal side effects. The scores noted on the SA scale are similar to that found with placebo (Simpson & Angus 1971).

Clinical chemistry and hematology were performed weekly. Modest elevations of alkaline phosphatase (three patients), SGOT (four patients), and LDH (four patients) were noted. These gradually returned to normal after the drug was discontinued, or other neuroleptics substituted.

No significant changes were observed on blood pressure, pulse, weight, ECG, or EEG.

A number of adverse events noted in the study were judged to be drug related. These were as follows (number of patients in parentheses): seizure (1), fatigue (3), sleepiness (3), nausea (2), tremor (1), headache (1), insomnia (1), anorexia (1), diarrhea (1), gas (1).

EXTRAPYRAMIDAL ASSESSMENTS

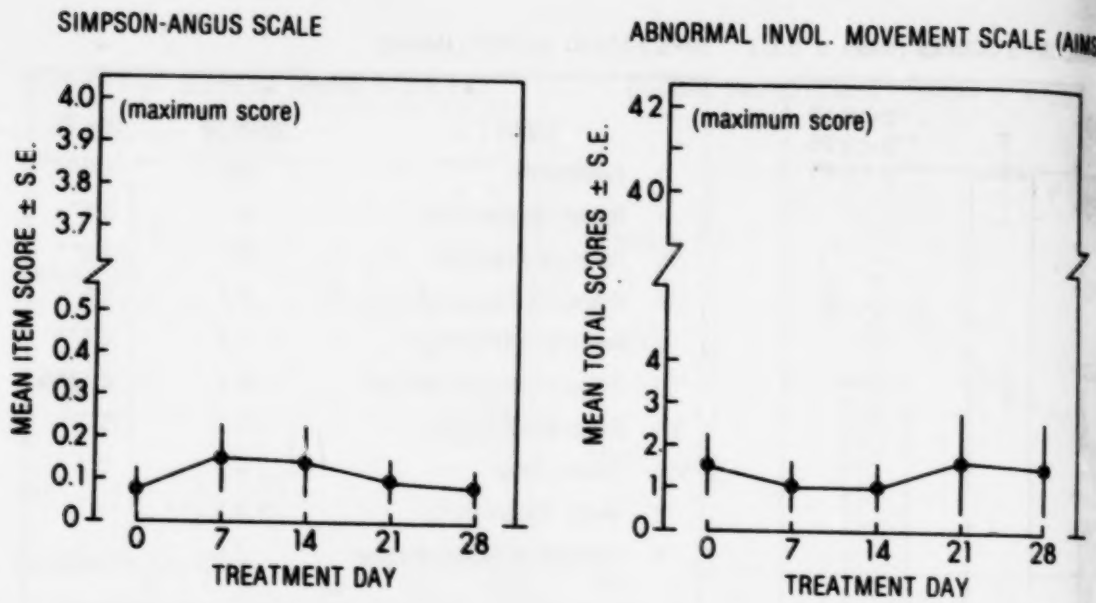


FIGURE 5

Summary

BW-234U is a well-tolerated antipsychotic agent in this acute schizophrenic population and has a low potential for inducing extrapyramidal or autonomic side effects. The efficacy which was seen needs to be confirmed by further controlled studies. The full dose range of this drug has yet to be determined.

References

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Does Long-Acting Injectable Neuroleptic Protect Against Tardive Dyskinesia?

Solomon C. Goldberg, Ph.D.[1] Ramakrishnan S. Shenoy, M.D.,[1] Demetrios Jullus, M.D.,[1] Robert M. Hamer, Ph.D.,[1] Beverly Ross, M.S.N.,[1] Teena Minton, R.N.,[1] and Marilyn Spiro, B.A.[1]

In an earlier study (Shenoy et al. 1981) of 34 chronic ambulatory schizophrenics who were maintained with fluphenazine decanoate for at least 2 years, an unusually low level of tardive dyskinesia was discovered compared to comparable patients reported in the literature. If anybody should have tardive dyskinesia, these patients should. It occurred to the authors that the patients might be suffering from a form of covert tardive dyskinesia that would become manifest only if medications were withdrawn. Since one major purpose of that study was to determine the effects on symptom status and tardive dyskinesia of discontinuation of drug therapy, there was the opportunity to see whether patients who initially showed no tardive dyskinesia would manifest any after being withdrawn from medication. Half the patients were randomly discontinued for a period of 6 weeks. Within that period, there was essentially no change in the level of tardive dyskinesia, either in the group that continued on medication or the random group that was withdrawn. Tardive dyskinesia was assessed by means of the Abnormal Involuntary Movements Scale (AIMS), a commonly employed instrument for this purpose. Inter-rater reliability was shown to be substantial.

That group of chronic ambulatory patients maintained on fluphenazine decanoate is part of a larger group of like patients who are maintained on a variety of oral neuroleptics. The patients on the long-acting injectable medication had been assigned to it years earlier because there had been problems in medication compliance with oral medication.

The obvious next step was to determine the level of dyskinesia in the larger group of patients on oral medication. If they showed the same low level, the results would be consistent, but puzzling. If they showed a higher level of tardive dyskinesia, the results would imply a protective or ameliorative mechanism in the injectable form of the medication.

[1]Medical College of Virginia, Richmond, VA 23298.

Patients

The patients were 76 primarily male chronic ambulatory schizphrenic patients who were maintained on a variety of oral neuroleptics for at least the past 2 years. Patients whose medications included antidepressants or lithium were not included in this sample. These patients lived in the community even though they occasionally manifested a moderate level of schizophrenic symptomatology. The patients had had multiple prior hospitalizations for schizophrenic episodes, even after being placed on maintenance medication.

Assessment of Tardive Dyskinesia

Symptoms of tardive dyskinesia were assessed by means of the Abnormal Involuntary Movements Scale (AIMS) developed for this purpose by the Psychopharmacology Research Branch of the National Institute of Mental Health (1975). Although the words "tardive dyskinesia" are not employed in the scale itself, the particular movements the observer has to record are those that have been identified in the literature pertaining to tardive dyskinesia in contrast to extrapyramidal side effects such as fine tremors, gross dystonic reactions, cogwheel rigidity, and akathisia. After a period of orientation and practice on nonstudy patients, the 76 patients were observed for tardive dyskinesia by one of three rating team pairs. Each rating team saw only a portion of the 76 patients.

Results

Reliability of Measurement

In observing the patients for tardive dyskinesia, one member of the rating team took the respon-

sibility for conducting the procedure and asking questions, while both members of the team rated the patient simultaneously. Rating team members would alternate conducting the examination. Immediately after a patient was rated, there was a postmortem comparison of the ratings given, but no changes were allowed to be made even if there were differences. Discussion of rating differences served as continuing training in the procedure and would hopefully have a beneficial effect on greater reliability on the subsequent occasions. Under these conditions, the rater agreement reliability by means of an intraclass correlation was .83 for global severity of tardive dyskinesia; for the sum of the seven specific items, intraclass correlation was .91. These levels of rater agreement compare favorably with those obtained on ratings of psychopathology.

Oral versus Depot Medication Maintenance on Tardive Dyskinesia

The Table shows the percent distribution of each item on the AIMS for the two medication groups. There is very obviously a greater prevalence of tardive dyskinesia in the group maintained on oral medications than in the group maintained on fluphenazine decanoate. The size of the significant differences in descending order are: a) tongue, b) face muscles, c) jaw, and d) eyes and perioral area. Nonsignificant differences were found for a) arms, wrists, hands, and fingers ($p = .089$) and b) legs, knees, ankles, and toes ($p = .26$).

Both age and duration of treatment were correlated with tardive dyskinesia. When entered as covarates, they reduced but did not eliminate the significant difference between medication groups. Measures of organicity in these patients were not available as another measure of risk for tardive dyskinesia.

Discussion

The results imply either that fluphenazine decanoate reduces the level of tardive dyskinesia if it is present, or protects against its development if not present.

If it is true that fluphenazine decanoate is less productive of tardive dyskinesia, what might the possible mechanism of action be? Baldessarini and Tarsy (1978) cite evidence supporting the interpretation that tardive dyskinesia "is associated with a state of relative dopaminergic overactivity or supersensitivity." This would account for worsening on withdrawal of dopamine-antagonistic neuroleptic drugs and worsening on administration of L-DOPA. Tune et al. (1980) found lower steady-state blood levels in patients who are maintained on long-acting injectable medication. It may then be that the oral medication is providing a higher steady-state blood level than is therapeutically required, bombards the post-synaptic receptors, and renders them "supersensitive." Tune et al. did not show a link between blood level and tardive dyskinesia, which now becomes a next obvious next step in research.

From a practical clinical point of view, the authors are not yet in a position to conclude that switching to the injectable form will reduce tardive dyskinesia. It is conceivable that the depot neuroleptic protects against the development of tardive dyskinesia if not present; but once tardive dyskinesia does become apparent, it may be persistent and hence may not be affected by switching to another form of medication. While the foregoing is possible, it is not a certainty, and the first and easier procedure to try on a patient with tardive dyskinesia would be a change to the long-acting form. In the context of a formal study, this would be done by randomly assigning a group with tardive dyskinesia who are being maintained on oral medication to a) either continuing on the oral, or b) changing to the long-acting form. However, for those practitioners who are not in a position to undertake formal research, they have nothing to lose by trying on an open, informal basis a change to long-acting medication in those patients suffering from moderate to severe tardive dyskinesia.

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Table

Percent Distributions of AIMS Items for Patients on Oral Neuroleptic ($N = 76$) vs. Fluphenazine Decanoate ($N = 31$)

Item	Absent	Minimal	Mild	Moderate	Severe	*P*
			Percent (rounded)			
1. Muscles of Facial Expression						
Oral neuroleptic	67	12	14	6	1	
Fluphenazine deconoate	98	2	0	0	0	.0004
2. Lips and Perioral Area						
Oral neuroleptic	50	16	11	13	2	
Fluphenazine decanoate	63	31	6	0	0	.0099
3. Jaw						
Oral neuroleptic	68	11	9	11	1	
Fluphenazine decanoate	92	6	2	0	0	.0041
4. Tongue						
Oral neuroleptic	38	22	26	10	5	
Fluphenazine decanoate	76	13	8	3	0	.0003
5. Upper extremities						
Oral neuroleptic	56	11	13	17	3	
Fluphenazine decanoate	66	13	18	3	0	.0898
6. Lower extremities						
Oral neuroleptic	72	9	11	7	1	
Fluphenazine decanoate	84	5	8	0	3	.2636
7. Neck, shoulders, hips						
Oral neuroleptic	86	5	3	3	3	
Fluphenazine decanoate	91	3	3	3	0	.5756
8. Global Severity						
Oral neuroleptic	22	37	22	16	3	
Fluphenazine decanoate	32	44	21	0	3	.0525
9. Incapacitation						
Oral neuroleptic	75	16	4	2	3	
Fluphenazine decanoate	81	16	0	3	0	.3634
10. Patients awareness of movements						
Oral neuroleptic	69	15	8	5	3	
Fluphenazine decanoate	53	29	15	3	0	—
Sum of Items 1-7:						
Oral neuroleptic						
Fluphenazine decanoate						.0005

Combined MAOI-Tricylic Antidepressant Treatment: A Controlled Trial

Kerrin White, M.D.,[1] Javad Razani, M.D.,[1] George Simpson, M.D.,[1] Ronald Rebal, M.D.,[1] R. Bruce Sloane, M.D.,[1] Judith O'Leary, M.A.,[1] and Ruby Palmer, R.N., M.A.[1]

The practice of combining monoamine oxidase inhibitor (MAOI) and tricyclic (TCA) antidepressants in treatment has been a source of controversy for nearly two decades. Case reports of severe reactions such as hyperthermic crises, delirium, and seizures led to widespread warnings against concurrent use of MAOIs and TCAs. However, reviewers raised many questions about these case reports, and uncontrolled clinical series on these treatments suggested both reasonable safety and unusually potent antidepressant effects. Until the past few years, no controlled clinical trials had been reported on these questions. The present study represents only the second such trial to use both double-blind methodology and random assignment to treatments.

This study was designed to assess whether combined treatment with tranylcypromine (TCP) and amitriptyline (AMI) has any pronounced advantages or disadvantages compared with single drugs used alone on a relatively heterogeneous group of depressed patients. The combined treatment followed an approach recommended by many clinicians who have used MAOIs and TCAs together: 1) first allowing a drug-free interval of at least 1 week; 2) then starting both drugs together, within the same day, at low dosage; 3) then gradually increasing dosage of both drugs together, to a maximum of half the dosage used with each single drug. This approach was compared with treatments involving the single drugs used alone at full dosage, so that patients in each treatment group would receive about equivalent amounts of "total antidepressant drugs," to avoid confusing simple summation of side-effects with unusual toxic drug interactions.

[1]Department of Psychiatry and the Behavioral Sciences, University of Southern California School of Medicine, Los Angeles, CA 90033.

Seventy-one inpatients and outpatients meeting Diagnostic and Statistical Manual-III (DSM-III) criteria for Major Depression were randomly assigned to a 4-week trial of double-blind treatment with either TCP, AMI, or the TCP-AMI combination. After a fixed starting dosage for the first week (either TCP 20 mg, q a.m., AMI 100 mg, q h.s., or TCP 10 mg, q a.m. plus AMI 50 mg, q h.s.), the treating psychiatrist could adjust dosage upwards on a weekly basis to maximum reached by the beginning of the third week (TCP 20 mg, t.i.d., AMI 300 mg, q h.s. or TCP 10 mg, t.i.d. plus AMI 150 mg, q h.s.).

Ratings of depressive symptoms by the patient and the treating psychiatrist were conducted weekly and included the Hamilton Depression and Anxiety Scales, the Clinial Global Impression, and the Zung Self-Rated Depression Scale. Monitoring for toxicity included a side-effect list completed weekly by the treating psychiatrist; frequent measurement of blood pressure, pulse rate, respiratory rate, temperature and weight; and repeated electrocardiograms, complete blood counts, serum electrolytes, liver function tests, and urinalyses.

Sixty patients completed the study; eleven dropped out prior to the end of the fourth week. Patients sometimes dropped out because of side-effects such as drowsiness or dizziness, but never because of life-threatening adverse reactions such as hyperthermic or hypertensive crises. The dropout rate was highest in the AMI-only group (24 percent) and lowest in the combined TCP-AMI group (5 percent).

There were no statistically significant differences between the three treatment groups at baseline on common demographic characteristics such as age, sex, or education; nor on clinical characteristics such as percentage of patients meeting RDC criteria for endogenicity or degree of symptom severity. Average maximum dosage was 40 mg/day TCP, 239 mg/day AMI, and in the combined treatment group 24 mg/day TCP and 128 mg/day AMI.

The psychiatrists, listing of side effects showed similar side-effect profiles for the three treatments. The most common side effects included dry mouth (72 percent of patients reported this), dizziness (61 percent), sedation (41 percent), and constipation (23 percent). Significant differences between the three treatments

were confined to a more frequent association of AMI with dry mouth (90 percent) and tremor (40 percent), and a less frequent association of TCP with anticholinergic effects as a group ($p < .01$). Blood pressure measurements suggested both resting and postural hypotension as effects of TCP, but only postural hypotension with AMI. The combined TCP-AMI treatment showed intermediate effects. Pulse rate and weight increases both seemed more pronounced with AMI.

On the four major outcome measures, patients on all three treatments improved to an equivalent degree at about the same rate. Improvement was moderate to marked for 76 percent on TCP, 75 percent on AMI, and 79 percent on TCP-AMI. Analyses of individual symptom items suggested superiority of TCP and TCP-AMI over AMI alone for hypochondriasis ($p < .01$ and $p < .03$, respectively), and superiority for AMI and TCP-AMI over TCP alone for insomnia ($p < .01$ and $p < .01$), as well as advantage for TCP over TCP-AMI on anxious mood ($p < .04$) and TCP over AMI on autonomic anxiety ($p < .05$).

These results indicate quite similar therapeutic and adverse effects for all three treatments. There is certainly no indication of either unusually severe toxicity or unusually potent efficacy for the MAOI-TCA combination as compared to the single drugs used alone. However, some differences in specific side effects and symptom improvement may have clinical relevance. For example, TCP may have an advantage in avoidance of anticholinergic side effects, while AMI or TCP-AMI may have an advantage for insomnia. As in prior research, there are suggestions of an MAOI advantage for "atypical" depressive symptoms such as hypochondriasis and anxiety.

These results support the relative safety of combined MAOI-TCA treatment when used according to specific guidelines such as were followed in this study. It should be emphasized that evidence for apparent safety does *not* extend to certain other ways of combining these drugs. For example, there is substantial case report evidence for hazards in the addition of a TCA to an established course of treatment with an MAOI.

Despite these indications of safety if the MAOI-TCA combination is used according to specific guidelines, there exists virtually no evidence from the few controlled studies to date for any major advantage to such combinations over rigorous treatment with single drugs or ECT. Nevertheless, there are suggestions from clinical experience that some patients refractory to adequate trials of the single drugs may still respond to their combination. This issue has yet to be addressed in controlled research.

For a complete review of the literature, see White and Simpson (1981).

Reference

White, K., and Simpson, G. Combined MAOI-tricydic antidepressant treatment: A reevaluation. *J. Clin. Psychopharmacol.*, 1:264-282, 1981.

Differential Efficacy of L-Deprenyl, a Selective MAO Type-B Inhibitor, in Endogenous and Nonendogenous Depression

J. John Mann, M.D.,[1] Allen Frances, M.D.[1] Eric D. Peselow, M.D.,[2] and Samuel Gershon, M.D.[3]

Introduction

Recent systematic studies have affirmed the value of classical nonselective monoamine oxidase (MAO) inhibitors as effective antidepressants. Overall these drugs appear effective in nonendogenous depression (Robinson et al. 1973) and perhaps some subgroup(s) of endogenous depression (Himmelhoch et al. 1972; Pare & Mack 1971). MAO inhibitors appear as effective as tricyclics for nonendogenous depression and perhaps superior for any associated anxiety symptoms (Ravaris et al. 1980). There is also evidence for a therapeutic effect in phobic disorders (Tyrer 1980). However, despite the usefulness of these agents, the risks of a hypertensive food or drug interraction, known colloquially as the "cheese" reaction, has remained as a deterrent to the use of MAO inhibitors.

The selective MAO type-A inhibitor clorgyline, although appearing to have antidepressant properties in unipolar patients (Wheatley 1970), also has a significant potential for the hypertensive "cheese" reaction comparable to classical MAO inhibitors (Lader et al. 1972). Therefore it is important to evaluate the MAO type-B inhibitors for safety and antidepressant potential. L-deprenyl is a potent selective MAO type-B inhibitor with a demonstrated safety advantage (Elsworth et al. 1978).

In this study, the effects of L-deprenyl were compared in endogenous and nonendogenous depression. We also monitored the degree of platelet MAO inhibition in order to evaluate whether the level of MAO inhibition would be a factor in determining clinical response in this study.

[1]Cornell University Medical College, Payne Whitney Clinic, New York, NY 10021.
[2]New York University Medical Center, New York, NY 10016.
[3]Wayne State University, Detroit, MI 48201.

Send reprint requests to: J. John Mann, M.D., Department of Psychiatry, Cornell University Medical College, Payne Whitney Clinic, 525 East 68th Street, New York, NY 10021.

Methods

Twenty-five patients who met Research Diagnostic Criteria for a major depressive disorder completed the study. The patients were subdivided into endogenous and nonendogenous subgroups using the Newcastle scale.

All patients underwent a single-blind placebo washout for one week to screen out strong placebo responders. Patients who still scored 16 or higher on the first 17 items of the Hamilton Depression Scale (HDS) then underwent 4 weeks of treatment with L-deprenyl. Patients were treated with initial doses of 5-10 mg per day for the first week, building up to a maximum of 15-20 mg per day through weekly dose increments depending on clinical response.

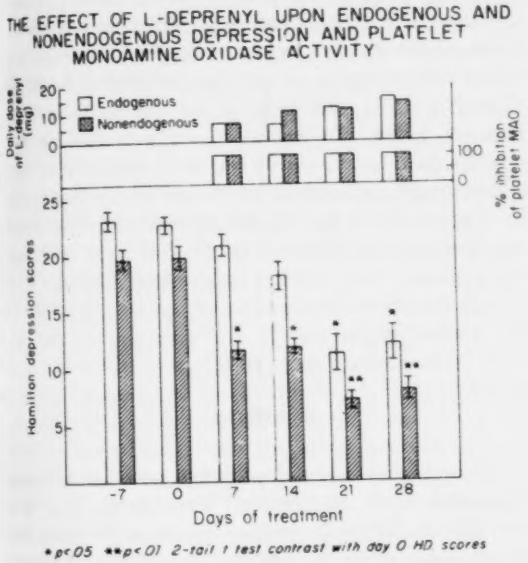
Results

Thirteen patients with endogenous depression and 12 with nonendogenous depression were studied. The groups did not differ significantly on age, sex ratio, and baseline severity of illness as measured by the HDS.

As shown in the Figure, both groups showed a statistically significant amerlioration of depression, but the onset of improvement appeared sooner in the nonendogenous group. The rate of dropout was greater in the endogenous group with three patients dropping out because of lack of therapeutic response and one because of hypomania.

If responders were defined by a >50 percent reduction in Hamilton Score or an endpoint score of ≤ 10 in the HDS, then the endogenous group had 6/13 responders and the nonendogenous group had 10/12 responders. The difference in the rate of responders between the two groups approached significance ($p<0.10$ Fisher Exact Probability Test). Five of seven patients responded in the bipolar endogenous group compared to 1/6 unipolar patients, a non significant difference.

All responders in the endogenous group and 9/10 of the nonendogenous responders had responded according to the above criteria by Day 21. There was a trend for the amelioration in the HDS score after only 1 week of active drug to be greater in the responder groups: (-4 ± 2.5 in the endogenous and -9.1 ± 2.3 in the nonendogenous) than in the nonresponders (-0.1 ± 1.4 and -3.5 ± 1.5), respectively, in endogenous and nonendogenous groups ($p<0.1$ and $p<0.05$, one-tailed t-test).


THE EFFECT OF L-DEPRENYL UPON ENDOGENOUS AND NONENDOGENOUS DEPRESSION AND PLATELET MONOAMINE OXIDASE ACTIVITY
Daily dose of L-deprenyl (mg)
Endogenous
Nonendogenous
% inhibition of platelet MAO
Hamilton depression scores
Days of treatment
*p<.05 **p<.01 2-tail t test contrast with day 0 HD scores

FIGURE

(From: Mann et al. *J. Clin. Psychopharmacology*, 2: 54-57, 1982.)

The degree of endogenicity or nonendogenicity as indicated by the Newcastle scale, or the duration of the illness, showed no significant linear correlation with the amelioration in the HDS score in either the endogenous or nonendogenous groups.

The Figure shows the degree of platelet MAO inhibition and the mean daily dosages of L-deprenyl in both groups. Deprenyl was a potent rapid inhibitor of platelet MAO. A 10 mg dose of L-deprenyl almost totally inhibited platelet MAO within 2 hours.

Baseline MAO activity showed no significant linear correlation with amelioration in HDS scores. However, baseline MAO activity of responders in the endogenous and nonendogenous groups was respectively 32.0 ± 6.6 and 24.5 ± 5.4 nmol/hour/mg protein, which, although not statistically higher than nonresponders (22 ± 2.9 and 17.3 ± 7.9), may prove to be significant in a study with greater numbers of patients.

Deprenyl produced several of the typical side effects of classical MAO inhibitors including increased energy, initial insomnia, reduced appetite, increased aggressive feelings, and agitation. However, no changes were seen in blood pressure or electrocardiograph (ECG). In particular, no patient developed significant orthostatic hypotension (a drop in systolic blood pressure of >20 mmHg). When each group was subdivided into responders and nonresponders, there were still no significant changes in blood pressure. In contrast to classical nonselective MAOIs, no patients developed impotence or peripheral edema.

Discussion

There is a body of evidence in the literature suggesting that classical MAO inhibitors such as phenelzine are more effective in nonendogenous rather than endogenous depression as a whole. Although this study had design limitations by being an open study, and involved relatively small numbers of patients, L-deprenyl did appear to have an antidepressant effect in nonendogenous depression and perhaps the bipolar subgroup of endogenous depression (in contrast to unipolar endogenous depressives) in a dose range that is reported to preserve selective MAO inhibition (Ekstedt et al. 1979; Reiderer & Reynolds 1980).

The use of selective MAO inhibitors, apart from creating the possibility of safer, more specific drugs, also permits a valuable alternative approach to the biochemical subclassification of depressive disorders. We are initiating double-blind controlled studies to examine the therapeutic spectrum of action of L-deprenyl and its efficacy in order to evaluate the potential biochemical heterogeneity of depressive disorders. Mendlewicz (1982) has recently reported that L-deprenyl was an effective antidepressant in a group of patients with major depression in a placebo-controlled, double-blind study.

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Pharmacological Treatment of Delusional Depressives[1]

Duane G. Spiker, M.D.,[2] Israel Hanin, Ph.D.,[2] James M. Perel, Ph.D.,[2] Jane E. Cofsky, M.S.W.,[2] Albert J. Rossi, M.D.,[2] and Denise Sorisio, B.S.[2]

Introduction

The optimal pharmacological treatment of patients with a delusional depression is not clear. Most of the studies reported in the literature are either retrospective or not double-blind (Avery & Winokur 1977; Moradi et al. 1979; Nelson & Bowers 1978). In addition, only a few of the studies measured plasma levels of the tricyclic antidepressant (Glassman et al. 1977). Consequently, a prospective double-blind study of delusional depressives, in which plasma levels of the antidepressant were measured, was initiated. This report describes the results of the first 2 years of the 3-year project.

Method

All subjects were inpatients on the Clinical Research Unit at Western Psychiatric Institute and Clinic (WPIC). At the time of admission, patients were given a traditional psychiatric interview and a complete physical examination. During the subsequent 7-day drug-free period, they underwent a variety of routine laboratory tests including thyroid function tests, an electroencephalogram, and any other tests indicated based on their history and physical examination. Any patient who was found to have a medical illness affecting his or her central nervous system was excluded from the study. All patients gave informed consent.

At the end of the 7-day drug-free period, the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott & Spitzer 1978) was com-

[1]This study was supported in part by USPHS Grant MH-32707 from the National Institute of Mental Health.

[2]Department of Psychiatry, University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinic, Pittsburgh, PA 15213.

pleted using information from the initial interview, case records, collateral information from relatives, observation on the unit, and a second interview with each patient. The SADS is a structured research interview that collects information necessary to make diagnoses using the Research Diagnostic Criteria (RDC) (Spitzer et al. 1978). For inclusion in the study the patients had to meet the RDC for major depressive disorder, primary subtype. In addition, they had to meet the criteria for psychotic subtype based on the presence of a clear-cut delusion. The severity of depression was measured by the Hamilton Rating Scale (HRS), using the sum of two raters on the 17-item HRS (Hamilton 1960). Patients entered the study if the combined HRS score for two raters was 30 or more. After the 7-day drug-free period, the patients were randomly assigned to perphenazine, amitriptyline, or perphenazine + amitriptyline in adequate doses for 35 days. Blood collection and measurement of plasma levels of amitriptyline and nortriptyline were measured as previously described (Kupfer et al. 1977).

To date, 44 patients have entered the study and 36 have completed the 35-day project. Four patients left the hospital against medical advice for reasons unrelated to the protocol. Two patients developed an organic brain syndrome — one on perphenazine and one on amitriptyline + perphenazine. One patient became unmanageable on amitripyline. One patient was dropped because of medical problems unrelated to the study. The responses of the 36 patients who completed the study are shown in Table 1. Responders were defined as patients who no longer were delusional or depressed. Nonresponders were defined as patients who were either depressed, delusional, or both. The patients so far have been either clear-cut responders or clear-cut nonresponders.

Table 1

Response to Treatment

	Responders	Nonresponders
Amitriptyline	3	6
Perphenazine	2	11
Amitriptyline + Perphenazine	11	3

The role of amitriptyline and its metabolite nortriptyline in explaining why some delusionally depressed patients respond to amitriptyline and some do not is unclear. Of the nine patients on amitriptyline who completed the study, three were responders and six were nonresponders. Their plasma levels of amitriptyline and nortriptyline are shown in Table 2. The plasma level of 200 ng/ml of amitriptyline + nortriptyline was used because previous work at WPIC using the same methodology has shown that amitriptyline + nortriptyline ≥ 200 ng/ml is the effective level for treating nondelusional depressed patients (Kupfer et al. 1977).

Patients who were treated with amitriptyline + perphenazine had a mean plasma level of amitriptyline + nortriptyline of 297 ng/ml, while patients treated only with amitriptyline had a mean plasma level of 245 ng/ml.

Discussion

Although the sample size is still too small to make a definitive statement, some trends are apparent. The combination of the antidepressant and the antipsychotic appears to be the most efficacious with a 79 percent response rate. There are very clearly patients with a delusional depression who do respond to an antidepressant alone. There is also a suggestion that the response rate increases with increasing plasma levels of amitriptyline + nortriptyline. Interestingly, amitriptyline alone appears to be more effective than perphenazine alone. Whether the increased response rate of patients treated with amitriptyline + perphenazine can be explained by the increased amitriptyline + nortriptyline plasma levels, or whether the perphenazine has some additional effect, remains to be determined.

Table 2

Plasma Levels of Amitriptyline + Nortriptyline in Patients Treated with Amitriptyline

	Responders	Nonresponders
Amitriptyline + Nortriptyline ≤ 200 ng/ml	1	3
Amitriptyline + Nortriptyline ≥ 200 ng/ml	2	3

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Erythrocyte and Plasma Choline in Bipolar Psychiatric Patients: A Followup Study[1]

Israel Hanin, Ph.D.,[2] Bruce M. Cohen, M.D., Ph.D.,[3] Ursula Kopp,[2] and Joseph F. Lipinski, M.D.[3]

Introduction

Over the past four years there has been considerable interest in red blood cell (RBC) choline (Ch) as a potential cholinergic marker. Significantly elevated levels of RBC Ch have been reported in a subset of drug-free unipolar depressed patients (Hanin et al. 1980a); in drug-free bipolar manic patients (Jope et al. 1980); in patients with Gilles de la Tourette's Syndrome (Hanin et al. 1979); in a major portion of biological relatives of patients with Gilles de la Tourette's Syndrome (Comings et al. 1982); as well as in a segment of patients with Alzheimer's disease (Barclay et al. 1982, Friedman et al. 1981).

These elevated levels of RBC Ch are not drug induced; in fact, among the commonly used psychotherapeutic agents to date, only lithium has been shown to alter RBC Ch levels (Domino et al. 1981; Hanin et al. 1981; Jones & Kuchel 1980; Jope et al. 1978; Shea et al. 1981). This effect appears to be irreversible (Lee et al. 1974), and due to inhibition of efflux of Ch accumulated as a result of breakdown of membrane phospholipids on the inside of the RBC (Hanin et al. 1980b; Jenden et al. 1980).

The clinical significance of these elevated RBC Ch levels, whether endogenous or related to chronic lithium administration, is as yet not entirely understood. However, there still is a need for more well-controlled analyses to be conducted, and for reliable baseline data to be obtained (without any room for individual bias in interpreting the results), before one can move on to the

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[2]Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213.

[3]McLean Hospital Mailman Research Center, Clinical Biochemistry Laboratory, Belmont, MA 02178.

task of establishing any clinical relevance, or any potential biological marker role for RBC Ch *in vivo*. Hence the present studies, the results of which are reported in this paper.

Method

These results represent a collaborative effort between investigators from two institutions: Western Psychiatric Institute and Clinic Department of Psychiatry (WPIC), University of Pittsburgh School of Medicine (I.H. and U.K.); and the McLean Hospital Mailman Research Center, Laboratories for Psychiatric Research, in Belmont, Massachusetts (B.M.C. and J.F.L.). These studies were conducted for the purpose of establishing plasma and RBC Ch levels in a broad spectrum of manic-depressive patients, using a totally "blind" approach for data handling.

Patients were diagnosed and selected at McLean Hospital; blood samples were coded, processed, frozen, sent in dry ice packing to Pittsburgh, and stored at −20°C until preparation for analysis. Thawing, isolation, and analysis of Ch content in all samples was conducted in Pittsburgh. The results were then sent to McLean Hospital and decoded.

Patients selected for these studies were between 18 and 55 years old. They were admitted to the study on the condition that they had received no prior psychoactive medication for at least 1 month; no depot neuroleptic for at least 3 months; and no lithium for at least 6 months (except where specifically noted below). Patients were diagnosed by Diagnostic and Statistical Manual-III (DSM-III) criteria. They were excluded from the study if the presence of medical or neurological disease was noted.

On admission, patients were subjected to routine blood work (CBC, SMA-12, T4), urine analysis, ECG, EEG, chest X-ray, and a physical examination. This was followed by weekly determinations of complete blood count and SMA-12. Vital signs were taken daily. Subjects remained off all medications in the hospital for several days, during which blood was drawn for baseline Ch levels.

Blood (10 ml) was drawn in the morning after an overnight fast, into heparinized (green top) Venoject® tubes, and processed according to Hanin et al. (1980a). Subsequent analysis of plasma and RBC Ch was conducted using gas chromatography-mass spectrometry, according to Hanin and Skinner (1975).

In manic patients serial bloods were also drawn weekly for Ch determinations during treatment. Treatment with lithium alone, lecithin alone, or a combination of both are as noted in data shown below. Lithium carbonate was started at 300 mg b.i.d. Serum lithium levels were subsequently adjusted to 0.5-0.7 meq/l in the second week. Lecithin (Phospholipon 100, 30 g/day dissolved in ethanol) on ice cream was given to patients in three divided doses. Placebo for lecithin consisted of cod liver oil, castor oil, and ethanol.

Control subjects were drug-free, psychiatrically normal individuals, of the same age range as the patients.

Results

RBC and Plasma Ch levels: Drug-Free Manics vs. Controls

Table 1 shows values of plasma and RBC Ch levels measured in 18 drug-free bipolar disorder manic patients. Table 2 shows values of plasma and RBC Ch levels measured in 18 normal control subjects. While mean RBC Ch levels appeared to be higher in the manic patients, the values were not significantly different from RBC values in the control group ($t=1.04$; $N=34$). Also, the range of values was quite similar for both groups. Neither were plasma Ch levels significantly different between the two groups ($t=0.39$; $N=34$).

Effect of Lithium Treatment on RBC and Plasma Ch Levels

Results obtained with eight manic patients are shown in Table 3. Time of exposure of these patients to lithium varied between individuals. It is nevertheless clear that lithium treatment significantly elevated RBC Ch levels, while not affecting plasma Ch levels at all (Compare Tables 1 and 2).

Table 1

Plasma (P) and Erythrocyte (RBC) Choline (nmol/ml) in Bipolar Disorder Manic Patients Which Were Either Drug-Free or Treated With Neuroleptics, But Were Not Exposed to Lithium

Subject	Age	Sex	Meds	P Choline	RBC Choline
1	18	M		7.7	8.8
2	27	F		5.7	7.2
3	30	F		9.0	27.5
4	51	M		8.4	11.2
5	27	F		5.8	7.9
6	36	M	N	8.6	11.2
7	23	F		8.7	8.7
8	23	F	O	6.0	18.5
9	34	F		9.6	10.6
10	19	F	N	4.2	83.8
11	31	M		7.5	53.7
12	35	F	E	6.8	6.9
13	44	M		7.5	111.2
14	32	F		8.6	9.3
15	20	M		7.8	15.3
16	19	M		5.6	13.7
17	48	F		10.2	14.8
18	43	F		6.1	5.6

Mean ± SE: Plasma = 7.4 ± 1.1; RBC = 23.7 ± 6.9

Table 2

Plasma and Erythrocyte (RBC) Choline (nmol/ml) in Normal Control Subjects

Subject	Age	Sex	Meds	Plasma Choline	RBC Choline
1	18	M		8.8	21.2
2	25	F		7.5	9.2
3	27	F		7.5	9.7
4	29	M		6.8	8.6
5	28	F		5.1	7.6
6	24	M		7.8	7.5
7	23	F	N	7.9	7.8
8	24	M		6.2	7.4
9	29	M	O	8.9	12.3
10	23	F		7.9	8.5
11	26	F	N	7.0	32.0
12	39	F		5.6	5.2
13	22	M	E	10.5	12.8
14	18	M		7.1	75.5
15	30	M		7.3	23.2
16	25	F		6.9	9.2
17	26	M		7.2	8.3
18	34	M	Hydrochlorthiazine	11.4	10.1

Mean ± SE for Normal Controls: Plasma = 7.8 ± 0.4, RBC = 15.3 ± 3.9

Table 3

Plasma and Erythrocyte (RBC) Choline (nmol/ml) in Bipolar Disorder, Manic Patients, Treated with Lithium[a]

Subject	Age	Sex	Plasma Choline	RBC Choline
1	26	M	6.9	378.0
2	18	M	8.9	311.5
3	25	F	7.2	103.3
4	24	M	5.0	694.3
5	28	M	5.8	175.7
6	22	F	5.7	334.4
7	20	F	6.2	112.8
8	21	M	7.6	59.6

[a] Exposure to lithium varied within individual patients. Mean ± SE for above patients on lithium: Plasma = 6.6 ± 0.4; RBC = 256.2 ± 79.0.

Effect of Lecithin Alone, or Concurrent with Lithium and Other Drugs on Plasma and RBC Ch Levels

Table 4 demonstrates the effect of lecithin treatment on plasma and RBC Ch levels. Subjects were concurrently drug-free, or treated with another psychotropic agent, as specified in the Table.

Although variable, and shown only in the case of four individuals, the measured changes in plasma and Ch levels are important for purposes of interpreting the role of the RBC as a Ch carrier *in vivo*. (*See* Discussion)

Discussion and Summary

The data reported in this paper confirm some of our earlier findings; disagree with others reported in the literature; and also provide some new intriguing observations which will require further experimentation and analysis. Although preliminary, the authors believe that these findings were well worth reporting, particularly because of the "double-blind" circumstances inherent in the generation and analysis of the data.

The results reported in this paper allow for the following conclusions:

1. *In drug-free manics RBC Ch and plasma Ch levels are not statistically different from the respective values found in controls.* The authors' data thus are in contradiction to Jope et al. (1980), who reported

elevated levels of RBC Ch in patients diagnosed as manic, prior to lithium therapy. Shea et al. (1981) have also reported that there was no significant difference in RBC Ch between lithium-free patients with affective disorder and normal subjects. Unfortunately the number of drug-free bipolar manics in this group of patients was not identified.

At present there is no clear explanation for the discrepancy in these reported results. The differences could not be attributed to methodologic variances since both Hanin and co-investigators, and Jope and co-investigators used an essentially identical gas chromatograph-mass spectrometric technique for the analysis of RBC Ch levels, while Shea and co-investigators used a radioenzymatic assay. Conceivably, the differences could be due to the fact that, once lithium treatment is discontinued, drug-induced elevated RBC Ch levels require over 4 months (essentially the life-time of the RBC) to return to normal (Hanin et al. 1980b). Thus, any prior exposure to lithium within 4 to 5 months of the analysis in any of the five patients used by Jope and co-investigators could explain the elevation in RBC Ch levels as reported by these investigators. In the present studies extra precautions were taken to exclude from the protocol any patient who had been exposed to lithium within 6 months of the time of the analysis for RBC and plasma Ch levels. Further studies with a large number of patients may resolve this question.

2. *Lithium treatment significantly elevates RBC Ch levels.* This finding confirms earlier reports from the laboratories of Jope, Jones, Hanin, Domino, Shea, and others.

3. *Plasma Ch is not significantly affected by lithium treatment.* Shea et al. (1981) did however report significantly elevated levels of plasma Ch in samples obtained from lithium-treated patients. These investigators state that it is possible that the plasma was contaminated by RBC, although any plasma samples with a tinge of red were discarded. In any case, the elevation in plasma Ch levels observed by Shea and co-investigators was only twofold at best, while RBC Ch levels were elevated more than tenfold.

4. *Treatment of patients with lecithin elevates plasma Ch levels, irrespective of whether RBC Ch levels are concomitantly in the "normal" range, or abnormally elevated due to lithium therapy.*

This finding, in conjunction with data summarized above, suggests separate physiological roles for Ch in plasma and in RBCs. The findings suggest that both compartments in blood should be considered as separate, yet interdependent, entities in their function as carriers of Ch from blood to other tissues, *in vivo*.

Table 4

Plasma (P) and Erythrocyte (RBC) Choline (nmol/ml) in Patients Before and After Receiving Lecithin

Subject	Age	Sex	Lecithin	Other Medications	Plasma Choline	RBC Choline
A	18	M	None	Haldol, Artane	9.6	10.2
			On × 4 days	Haldol, Artane	13.5	16.3
			Off × 5 days	Haldol, Artane	5.9	7.1
			Off × 10 days	Haldol, Artane	9.3	7.2
			Off × 17 days	Lithium × 6 days	9.3	126.2
B	26	M	None	Tril, Artane, Lithium	6.9	376.0
			On × 10 days	Tril, Artane, Lithium	29.1	682.2
			Off × 8 days	Tril, Artane, Lithium	10.1	462.7
C	33	F	None	None, but on lithium	6.5	127.5
			On × 1 days	within a few months	23.8	127.8
			On × 10 days	of admission	25.1	203.6
D	22	F	None	Mellaril, Lithium	5.7	334.4
			On × 7 days	Mellaril, Lithium	19.3	259.4

It is anticipated that future studies will ascertain whether the extent of normal exchange of Ch between plasma and RBC in blood will, in turn, predicate the amount of free Ch available to key physiological sites *in vivo*; such as the cholinergic nerve terminal for the synthesis of acetylcholine. Previous studies by Hanin et al. (1980b) have clearly demonstrated that Ch exchange between plasma and RBC is inversely proportional to RBC Ch levels. In clinical situations where endogenous RBC Ch levels have been shown to be higher than normal, this could reflect deviations from normal in the extent of availability of Ch to central nerve terminals crucial for acetylcholine synthesis *in vivo*.

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Relationship Between Cognition and Mood in Geriatric Depression

Barry Reisberg, M.D.,[1] Steven H. Ferris, Ph.D.,[1] Anastase Georgotas, M.D.,[1] Mony J. de Leon, Ed.D.,[1] and Michael K. Schneck, M.D.[1]

The interrelationship between cognition and affect among geriatric depressed patients is an area of major clinical and therapeutic importance. The clinical importance of this relationship derives from the need to differentiate geriatric depression and Primary Degenerative Dementia (PDD), the two major psychiatric disorders of the elderly. Current evidence indicates that depressed patients do not demonstrate marked global cognitive deficits (Friedman 1964; Neville & Folstein 1979; Sternberg & Jarvik 1976). However, depressed patients do rate themselves more negatively in cognitive and other areas (Friedman 1964), and may demonstrate deficits in circumscribed cognitive areas, notably on attention and immediate memory tasks (Neville & Folstein 1979; Sternberg & Jarvik 1976). Because of the potential importance and implications of the relationship between geriatric depression and cognition, we examined the correlation between magnitude of both self-rated and clinically rated depression and the magnitude of cognitive deficit in elderly outpatients.

Method

Twenty-two outpatient volunteers (mean age 64.8 ± 4.5 years) with subjective complaints of depression were accepted for the study. They met all of the following criteria after treatment with placebo for 7 days: 1) 60 to 85 years of age; 2) a score of 18 or more on the 17-item Hamilton Rating Scale (Hamilton 1960); 3) a Wechsler Adult Intelligence Scale Vocabulary Score ≥ 8 (Wechsler 1941); 4) at least five symptoms of Depressive Affective Disorder, Diagnostic and Statistical Manual-III (DSM-III) diagnoses 296.2, 296.3, 296.5, 296.6, or 300 (American Psychiatric Association 1980), including depressed mood; 5) clinical laboratory evaluations within ± 10 percent of the normal range. Patients were excluded if they had a history of, or active symptoms indicating: 1) central nervous system (CNS) infection, neoplasm, or evidence of progressive neurologic disease other than PDD; 2) epilepsy; 3) schizophrenia; 4) alcoholism or drug dependence; 5) other psychiatric conditions which prevented the subject's cooperation in the study; or 6) major medical illnesses including uncontrolled congestive heart failure, uncontrolled diabetes mellitis, chronic pulmonary insufficiency, or severe angina.

The patients were assessed with respect to clinical and psychometric parameters. The degree of memory impairment was assessed using the Guild Memory Scale (Gilbert et al. 1968; Gilbert & Levee 1971). Normative values are available for each of the five subtests of the Guild with respect to age and intelligence level as estimated by the Wechsler Adult Intelligence Scale (WAIS) vocabulary score of the subject (Crook et al. 1980). Additional cognitive measures included assessment of primary (short-term) memory, digit span forward and backward; secondary (long-term) memory; First and Last Names (French et al. 1974); Memory for Faces (Ferris et al. 1980); and perceptual-motor tasks: Perceptual Speed (Moran & Mefferd 1959), Simple and Disjunctive Reaction Time (Ferris et al. 1976), and Finger-Tapping Speed (Lehmann & Ban 1970).

The clinical assessments included two psychiatric ratings, the Hamilton Depression Scale, and the Inventory of Psychic and Somatic Complaints in the Elderly (IPSC-E) (Raskin & Crook 1977); and two self-ratings, the Beck Depression Inventory (Beck et al. 1961), and the Mood Scale for the Elderly (MS-E) (Raskin & Crook 1976). Pearson correlation coefficients were computed between the psychiatrist-rated or self-rated clinical assessments and the psychometric test performance scores.

Results

Based upon the norms for the Guild Memory Test, nine subjects were above average in memory, seven were below average, and six were one standard deviation or more below average.

[1]Geriatric Study and Treatment Program, Department of Psychiatry, New York University Medical Center, New York, NY 10016.

No subjects demonstrated more than mild global cognitive deterioration as defined on the Global Deterioration Scale (GDS) for PDD (GDS ≤ 3), an instrument for which Guild and clinical rating criteria are available (Reisberg et al. 1982). Hence, depressive affective disorder was not associated with marked cognitive impairment in these elderly outpatients.

There were no statistically significant correlations between total Hamilton scores and any of the psychometric test scores. For the IPSC-E, the total score on the depression cluster, (Items 8 through 14) correlated only with simple reaction time ($r = .51$, $p < .05$). When total IPSC-E Depression scores were combined with related assessments of Energy Loss (Items 1 through 7), Sleep Disturbance (Items 15 through 17), and Anxiety-Tension (Items 18 through 25), no significant correlations with performance on any of the psychometric tests were observed. Total self-assessment scores on the Beck Depression Scale also failed to correlate significantly with any of the psychometric test scores. Self-assessments of negative mood on the MS-E correlated with poor performance on four of the psychometric measures (*see* Table). The strongest relationship ($r = .68$, $p < .01$), was observed for slowing of simple reaction time.

Conclusions

Our findings with respect to the magnitude of cognitive impairment in geriatric depressed outpatients are consistent with the findings of previous investigators with respect to both adult depression (Friedman 1964; Sternberg & Jarvik 1976) and geriatric depression (Neville & Folstein 1979). Specifically, geriatric patients with clinically significant depression actually perform better than average (41 percent of our sample), or only slightly below average (32 percent), on assessments of memory. Hence, the overall magnitude of cognitive impairment associated with geriatric depression in most patients is not large.

However, sensitive clinical mood assessment instruments and cognitive tests are capable of demonstrating some significant relationships between magnitude of depression and psychometric performance. These relationships occurred only for measures such as reaction time, perceptual speed and motor speed, but not for measures of memory function. Since these tests are measures of attention or alertness, our results are consistent with earlier findings suggesting attentional, rather than memory deficits in geriatric depressed patients (Neville & Folstein 1979). Self-ratings of dysphoric mood on the MS-E were found to relate more strongly to impaired psychometric performance than psychiatrist's assessments of the magnitude of dysphoric symptomatology.

We have previously found that in patients with early symptoms of age associated cognitive decline or PDD, psychometric deficits of a global nature tend to accompany progression of the disorder (Reisberg et al. 1981). Hence, the patterns of psychometric impairments in geriatric depression and in PDD do appear to differ. Further work is needed to determine if these patterns are of differential diagnostic significance.

Table

Significant Pearson Correlations Between MS-E Self-Assessments and Psychometric Indices ($N = 22$)

Measure	Combined MS-E Global Score
Digit Span	
Forward	
Backward	.46[a]
Names	
Trial 1 - Correct	
Trial 2 - Correct	
Trial 3 - Correct	
Delay - Correct	
Faces	
Trial 1	
Trial 2	
Trial 3	
Perceptual Speed	
Correct	.43[a]
Errors	
Reduction Time	
Simple	.68[b]
Disjunctive	
Finger-Tapping Speed	
Dominant Hand	.48[a]
Non-Dominant Hand	

[a] Significant at .05 level (two-tailed)
[b] Significant at .01 level (two-tailed)

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Cerebrospinal Fluid Acetylcholine, Choline, and Senile Dementia of the Alzheimer's Type[1]

Kenneth L. Davis, M.D.,[2] John Y-K. Hsieh, Ph.D.,[2] Michael I. Levy, M.D.,[2] Thomas B. Horvath, M.D.,[2] Bonnie M. Davis, M.D.,[2] and Richard C. Mohs, Ph.D.[2]

Degeneration of cholinergic neurons and formation of neurofibrillary tangles and senile plaques are characteristic findings in postmortem studies of patients with senile dementia of the Alzheimer's type (SDAT). The extent of these changes corresponds with the degree of memory loss as measured by psychometric tests such as the Memory Information Test (MIT) (Blessed et al. 1968). Brain samples from patients with SDAT display a significant loss of choline acetyltransferase (CAT) activity (Davies 1979), indicating that SDAT can be characterized by a deficit in central cholinergic activity. However, diminished dopaminergic, noradrenergic, and serotoninergic activity have all been implicated in SDAT, (Bowen et al. 1979; Carlsson et al. 1980) though not with the consistency of the cholinergic abnormality. Improved memory test performance following the administration of cholinergic drugs to patients with SDAT suggests that the cholinergic deficit is involved in the cognitive abnormalities of this disease (Davis et al. 1981). The present study was undertaken to determine whether cerebrospinal fluid (CSF) acetylcholine (Ach) concentrations and/or the concentrations of the major CSF metabolites of dopamine, norepinephrine, and serotonin are related to the severity of dementia in patients with SDAT.

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[2]Department of Psychiatry, Veterans Administration Medical Center Bronx, NY and Mount Sinai School of Medicine, New York, NY 10468.

Address correspondence to: Kenneth L. Davis, M.D., Chief of Psychiatry Service, VA Medical Center, 130 W. Kingsbridge Road, Bronx, NY 10468.

Methods

Ten males and four females, ages 53-80, who met Research Diagnostic Criteria for primary dementia/SDAT were entered in the study (Spitzer et al. 1978). Prior to entry particular attention was given to ruling out multi-infarct dementia, depression, alcoholism, and other medical causes of dementia. The MIT was administered by a trained rater prior to the lumbar puncture. The lumbar puncture was performed at 9:00 a.m. with the patient in recumbent position after 10 hours of bedrest. No medications had been given except an occasional dose of chloral hydrate to some patients for 2 weeks prior to the lumbar puncture.

CSF was collected into a dry ice bath and immediately frozen at −70°C for storage. The first through fifth milliliters of CSF were analyzed by gas chromatograph/mass spectrometry (GCMS) for acetlycholine and choline (Jenden et al. 1973). All reagents were distilled twice before conducting the assay. This assay has a minimum sensitivity of approximately .025 nanomoles/ml. The interassay variability is 16 percent for Ach, and 7 percent for choline. The intraassay variability is 16 percent for Ach, and 9 percent for choline. Values derived from this procedure are in agreement with previous published data (Welch et al. 1976). The sixth through twelfth milliliters were analyzed for homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5-HIAA) and 3-methoxy-5-hydroxyphenylethyleneglycol (MHPG) (Anderson et al. 1979, Karoum et al. 1975).

Results

The Pearson correlation coefficient of MIT scores with CSF acetylcholine levels was $r=0.76$ ($p<.005$). Thus, patients with the most impaired memory functioning tended to have low acetylcholine concentrations in the CSF (*see* Table). There was a nonsignificant trend for CSF choline to increase as the severity of the dementia increased. The ratio of choline/Ach was inversely correlated with the severity of the dementia to a significant degree ($r=-0.79$, $p<.001$). There was no significant correlation of CSF levels of HVA, 5-HIAA, or MHPG with the severity of dementia.

Table

CSF Measures in AD/SDAT

Patient	Age	MIT[a]	Ach Nanomoles/ML	Choline Nanomoles/ML	5-HIAA Nanograms/ML	HVA Nonograms/ML	Ratio of Choline/Acetylcholine	MHPG NG/ML
1	64	0	.026	3.26	29.0	38.0	125.4	8.6
2	62	1	.035	4.43	33.0	37.0	126.6	9.9
3	57	3	.046	3.02	33.8	80.4	65.7	7.6
4	53	6	.037	2.65	36.2	71.6	71.6	6.9
5	63	13	.049	2.78	26.0	50.4	66.7	---
6	62	0	.028	3.60	25.5	52.6	128.6	14.4
7	72	13	.058	3.05	15.7	17.8	52.6	5.9
8	57	7	.068	3.34	22.2	37.3	49.1	8.9
9	70	0	.029	2.35	22.0	38.8	81.0	6.2
10	59	1	.026	3.50	34.6	47.5	134.6	12.8
11	80	0	.038	3.80	27.0	21.0	100.0	8.7
12	75	10	.047	3.40	---	---	72.3	10.5
13	54	7	.035	3.23	---	---	92.3	10.1
14	78	12	.071	3.23	---	---	45.5	---
$\bar{X}$			.042 ± .004	3.26 ± 0.14	27.7 ± 1.9	44.7 ± 5.7	85.9 ± 8.6	9.2 ± 0.7

[a]MIT = Memory Information Test

Discussion

The results provide further evidence of the importance of the cholinergic deficiency in SDAT. Postmortem studies of patients with SDAT have emphasized the highly selective degeneration of cholinergic neurons, citing normal levels of synthetic enzymes associated with other neurotransmitter systems (Davies & Maloney 1976; Perry et al. 1977). The absence of a correlation of dementia with HVA, 5-HIAA, and MHPG levels here corroborates those studies.

The correlation of CSF Ach concentrations with severity of dementia as assessed by a histopathologically validated instrument represents the first biological antemortem reflection (excluding surgical brain biopsy) of the extent of illness in patients with SDAT. The crucial role of cholinergic activity in the memory deficit of SDAT is supported by this finding. Future applications might include predicting response to potential cholinomimetic drug treatments based on CSF Ach level, and monitoring the progression of the illness longitudinally. Measurement of CSF Ach in other types of dementia may yield data useful clinically in differential diagnosis.

Summary

Concentrations of several neurotransmitters and metabolites were measured in the CSF of patients with SDAT. CSF Ach concentration correlated significantly with memory test scores in these patients. There was no correlation with several other neurotransmitter metabolites.

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Cognitive and Performance Deficits in Depression

Allen Raskin, Ph.D.,[1] Alfred S. Friedman, Ph.D.,[2] and Alberto DiMascio, Ph.D.[3]

Among the characteristics most often cited as behavioral correlates of depressive illnesses are (a) disturbed psychomotor activity involving retardation or agitation, (b) ideational disturbances such as limitations of span of attention, slowness of thought processes, and learning impairment, (c) self-depreciation which is reflected by a lowering of level of aspiration and feelings of inadequacy, and (d) energy diminution with loss of drive and motivation (Ayd 1961; Lehmann 1965).

Empirical studies have not been uniformly successful in documenting these behavioral correlates of depression. For example, with regard to psychomotor functioning such as simple reaction time, investigators have found both no difference among normals and depressed patients (Hall & Stride 1954), and depressed patients to be slower than normals (Huston & Senf 1952). A similar situation obtains with regard to learning and other cognitive functions. For example, one study reported short-term memory deficits in depression (Sternberg & Jarvik 1976) whereas another failed to find impairment in short-term memory (Henry et al. 1973).

These inconsistencies across studies have been attributed to differences in the types and severity of illness of depressed patients admitted to these studies as well as the differences in how certain functions, such as short-term memory, are defined and assessed.

The general aim of the present study was to determine what effects, if any, the presence of moderate to severe depression has on tests sampling the aforementioned behavioral correlates of depression. The differential effects of age and sex on these measures was also examined.

[1]National Institute of Mental Health, Rockville, MD 20857.
[2]Philadelphia Psychiatric Center, Philadelphia, PA 19104.
[3]Boston State Hospital, Boston, MA 02124.

Send reprint requests to: Allen Raskin Ph.D., Pharmacologic and Somatic Treatments Research Branch, NIMH, Room 10C-14, 5600 Fishers Lane, Rockville, MD 20857.

Method

Patients

The study sample consisted of 277 patients drawn from three State hospitals (Boston State Hospital, Boston, Mass., Rochester State Hospital, Rochester, New York, and Rochester State Hospital, Rochester, Minn.) and two private institutions (Hartford Hospital, Hartford, Conn., and Philadelphia Psychiatric Center, Philadelphia, Pa.).

For admission, patients had to be newly hospitalized, between 16 and 70 years of age, and with no evidence of mental deficiency, chronic alcoholism, liver damage, unequivocal brain damage, cardiovascular disease, or epilepsy. Project coordinators (a psychiatrist or psychologist) at each hospital also rated patients on amount of depression in verbal report, behavior, and secondary symptoms of depression. Each of these three items were rated on 5-point intensity scales. For admission to the study, a patient had to achieve a total score of at least nine, which would be the equivalent of a moderate amount of depression.

Normals

The 112 normal subjects were drawn from the same institutions as the patients and matched to the patient sample on age, sex, and years of schooling (*see* Table 1). Although not noted in Table 1, there was also no significant difference between normals and patients on the vocabulary subtest of the Wechsler-Bellevue Intelligence Scale II. The normal subjects were between 16 and 60 years of age and the same exclusion criteria previously cited for the patients were applied to normal subjects. In addition, a normal subject could not be receiving in- or outpatient treatment for a medical disability, be a discharged mental patient being followed in an aftercare clinic, or be undergoing psychiatric treatment. These subjects also had to meet Diagnostic and Statistical Manual-II (DSM-II) criteria for No Mental Disorder (DSM-II diagnosis 318).

Table 1

Identifying and Background Characteristics of Study Sample

	Patients	Normals
Number	277	112
Age (Median)	41	42[a]
Sex (% female)	68	66[a]
Years Schooling (median)	11	12[a]
Neurotic Depression (%)[b]	51	
Psychotic Depression (%)[b]	38	
Schizoaffective (%)[b]	11	
Anxious Depression (%)[c]	29	
Withdrawn-Retarded Depression (%)[c]	20	

[a]None of the differences between the two groups on these demographic variables were statistically significant.
[b]Based on diagnoses in the Diagnostic and Statistical Manual-II.
[c]Based on depressive subtypes developed by John E. Overall.

Measures

There were 13 separate tests in the test battery yielding a total of 33 scores. A brief description of each test follows:

Psychomotor Performance. (a) Tapping. The rate of a simple repetitive movement is determined under both a "free" or non-speed condition, and a maximum speed condition. For each condition the number of taps in a 30-second period is recorded. After each trial, the subject is asked to estimate how many taps she or he did. (b) The Area Tapping Test (Foulds 1961). On this test, Caine (1960) found depressives to be constricted and cover less area on the paper than non-depressed individuals. The subject is instructed to make dots with a pencil on a piece of 8½ × 11" paper for a period of 1 minute. An 8½ × 11" clear stencil divided into squares indicates the total number of squares containing dots. (c) Circle Tracing Test. The Circle Tracing Test (Siegman 1961) is considered to be a test of the subject's impulse control level (motor-inhibition capacity). The subject is instructed to "trace this circle. . . as slowly as possible." The score is the time taken to complete the tracing. (d) Aiming. This paper and pencil visual-motor coordination test from Moran and Mefferd's (1959) battery involves the placing of a dot in the center of a series of circles 2mm in diameter. The number of dots placed completely within the circles, in each of four 30-second consecutive testing periods, and the number of errors (dots touching the edges or outside the circle), are recorded. After the task has been completed, the patient is asked to estimate the percentage of the time he was completely within the circle.

Measures of Ideational, Perceptual, and Cognitive Functioning. (a) Nonsense-syllable learning task. This task requires both learning and immediate recall. A list of 10 three-letter consonant nonsense syllables to be learned are presented on a memory drum. The syllables are presented twice, each for 3 seconds, in two different orders. A 1-minute task is then interposed. At its completion, the subjects are instructed to recall and write down correctly as many of the syllables as possible. The number of syllables recalled or attempted are recorded; the number of those that are correct recalls are also recorded. (b) The Gorham Proverb Test (1956). This test is used to assess verbal comprehension and abstract conceptualization. The subject's task is to give the meanings of proverbs. Thirteen items from Gorham's 40-item multiple-choice form of the test were selected for this study. From among four possible interpretations, the patient is to choose the best answer. These answers are ordered on the answer sheet from most abstract to most concrete. Three scores are obtained: an "Abstract" score, a "Concrete" score, and the combined "Adjusted" score. No time limit is imposed. (c) Unpaced Digit-Symbol Substitution Test. This test is a measure of incidental memory and learning. The Wechsler-Bellevue Intelligence Scale-II 2-minute subtest was used. The number of digit symbol substitutions and the number of errors made, in each of four consecutive 30-second periods, was recorded. (d) Paced Digit-Symbol Substitution Test. The paced digit-symbol test is similar to the regular or unpaced test with the exception that the numbers, rather than being presented on the sheet on which the symbols are to be written, are presented by means of a memory drum. The numbers are presented at the rate of 40 per minute, i.e., at 1½-second intervals. Because of the added pressure to respond within a specified time, it was felt that depressed patients would have more difficulty with paced tasks than with unpaced tasks. Three scores are derived from this test, the number of correct symbols, the number of errors, and the number of

omissions. (e) Estimating Dots. This is a technique developed by Fisher, Williams, and Lubin (1957) that is considered to be a measure of self-adequacy or, conversely, of uncertainty of judgment. Subjects are shown a series of 10 cards each containing a large number of dots. After each presentation of a card, for 10 seconds, the subject is asked to estimate the number of dots on the card shown and then to reevaluate his estimate and to indicate by how many dots he felt he was in error. (f) Time Estimation. This task taps the ability to experience perceptual phenomena in the absence of external cues. Two procedures are employed. First, the subject is asked to estimate how many seconds have elapsed between two signals (i.e., "start" and "stop"). A 15-second interval between the two signals is employed. Next, the subject is required to give a signal (i.e., "stop") when 15 seconds has elapsed after the signal to "start" has been given. The two times, in seconds, are recorded. (g) Shift Test (Friedman 1964). This task taps flexibility of mental set or maintenance of motivation to a boring routine task, and involves circling a specified digit whenever it occurs (irregularly) on a page of digits, and then shifting on command to circle a different digit and discontinue circling the previous digit. This is a 1½-minute task, requiring three shift commands, each of 30-second duration. The number of digits completed in each 30-second period is recorded. (h) The Stroop Color-Word Interference Test (1935). This test is used to assess conceptual set and flexibility. The subjects are presented a card containing 50 color-name words printed in a colored ink that is incongruous with the printed name. The subjects' task is to name the color of the ink in which the color-name words are printed. The score is the time taken to name the 50 colors on the card. The number of wrong responses is also recorded. (i) Clock Reversal Test. This is also a test of perceptual flexibility. The first two trials of this task merely require the subject to read the times on two cards (with hands but without numbers) indicated by the position of the hour and minute hands. In the third trial, the subject is not shown a card but told to imagine where the hour and minute hands would be if 12:30 were reversed. In the final trial, the subject is asked to reverse 3:20. Each of the four parts of this test are scored to indicate whether the subject gave the correct or incorrect response.

Testing was done soon after the patients' admission to the hospital and after patients had been off all psychoactive medication for a minimum of 4 days. In most instances, patients were kept off medication for at least a week prior to testing. The order of testing is indicated in Table 2. At the end of testing, test examiners completed a modified version of the Friedhoff Task Behavior Scale (Friedhoff & Alpert 1960). This test includes items sampling the patient's ability to cooperate and attend to the tasks. Patients who had considerable difficulty in attending or who were very uncooperative were dropped from the study. Total testing time was approximately 1 hour.

Statistical Analysis. A multivariate analysis of variance was used to test for group differences. Main effects in this model were group (patient vs. normal), sex, and age (under 40 vs. 40 and over). The score attained on the Vocabulary subtest of the Wechsler-Bellevue Intelligence Scale-II a continuous variable, was entered as a regression in the model. This model also generated three interaction terms, group by sex, group by age, and group by vocabulary score. Each main effect term was tested with the other main effects co-varied out. Hence, in the tests for differences between patients and normals the effects of age, sex, and vocabulary score were partialled out.

Table 2

Test Battery

Order of Testing
1. Tapping under free and speed conditions
2. Dot estimation (Fisher, Williams, & Lubin)
3. Aiming (Moran & Mefferd)
4. Time estimation
5. Unpaced digit symbol substitution (Wechsler)
6. Clock reversal
7. Shift test (Friedman)
8. Stroop Color-Word Interference Test
9. Area Tapping Test (Foulds)
10. Circle Tracing Test (Siegman)
11. Paced Digit Symbol
12. Learning and recall of nonsense syllables
13. Gorham Proverb Test

Results

Patients vs. Normals

There were significant patient-normal differences on 11 of the 13 tests and on 25 of the 33

scores derived from these tests. These results are presented in Table 3. The two tests that failed to show patient-normal differences were Time Estimation and Dot Estimation. Inter-individual variability for both patients and normals was very high on these tests which inflated the error terms and washed out patient-normal differences.

Table 3

Significant Differences Between Depressed Patients and Normal Controls on Cognitive and Psychomotor Tests

Variable	Mean Scores Patients	Normals	F-ratio
A. Tapping			
1. Free condition	69.65	55.93	10.28[b]
2. Additional taps under speed condition	54.17	75.22	25.07[b]
B. Aiming			
1. Total dots in circles	76.34	125.22	116.91[b]
2. Percentage accuracy-4 Trials	69.77	84.05	20.64[b]
3. Estimate by subjects of dots in circles	83.58	102.82	4.34[a]
C. Digit Symbol-Unpaced			
1. Correct symbols-Trial 2	12.07	17.00	76.07[b]
2. Percentage accuracy-Total	95.67	99.55	3.91[a]
3. Guess of time to complete test (seconds)	177.79	137.35	4.67[a]
4. Additional symbols completed Trial 4 vs. Trial 2	.36	1.73	5.26[a]
D. Digit Symbol - Paced			
1. Correct symbols	22.40	34.55	63.20[b]
2. No. errors	1.28	.47	4.20[a]
3. Percentage accuracy	69.56	86.10	20.32[b]
E. Clock reversal			
1. Trial 4 correct	1.77	1.90	4.39[a]
2. Score for speed and accuracy	2.49	3.82	25.45[b]
F. Shift Test			
1. Trial 3 (No. 4's crossed over)	15.88	21.72	62.39[b]
G. Stroop Color-Naming Test			
1. Total errors in reading	3.20	1.82	5.32[a]
2. Ratio of time to complete line 1, Card C and Card C total	16.42	14.28	9.23[b]
3. Critical difference score time to read Card C vs. Card B	42.34	34.07	6.62[a]
H. Area tapping			
1. Estimate of time to complete (seconds)	44.78	22.68	6.37[a]
I. Circle Tracing			
1. Time to trace (seconds) (slow time best)	43.35	68.55	16.35[b]
J. Learning nonsense syllables			
1. No. attempted	3.38	6.75	102.48[b]
2. No. correct	1.26	2.17	27.80[b]
K. Gorhams Proverbs Test			
1. Abstract sum	5.57	8.12	47.64[b]
2. Concrete sum	1.18	.59	18.06[b]
3. Abstract and concrete sum +6	9.68	13.53	57.13[b]

[a] Significant at .05 level (2-tailed).
[b] Significant at .01 level (2-tailed).

The number and breadth of the differences between patients and normals was surprising. A prior study by one of the authors (Friedman 1964) had found only modest differences between depressed patients and normals on psychomotor and cognitive tests, and most of these differences were on patient estimates of how well they did on the tests rather than in actual performance. Patients in the earlier study by Friedman (1964) were generally better educated than patients in the present study which may account, in part, for the differences in results between the two studies. The Friedman study also led us to expect patients to deprecate their actual performance on the tests by underestimating how well they did. Some evidence of this was apparent in their tendency to overestimate the time it took them to complete the unpaced digit symbol subtest which has a 120-second time limit, and in their estimate of time spent on the area tapping test. The actual time difference between patients and normals on the area tapping test was not significant under both the non-speed and speed conditions. However, it is also interesting that patients had fewer dots in circles in the Aiming Test than normals, and this difference was also reflected in their estimates of the number of dots they had placed in circles. Hence, in this instance their low estimate is an accurate reflection of their actual performance rather than an example of a low level of aspiration or feelings of inadequacy.

Table 4

Significant Age-Group Differences on Cognitive and Psychomotor Tests

Variable	Number	Under 40 Pt(1) 139	Under 40 Norm(2) 31	40 Plus Pt(3) 138	40 Plus Norm(4) 81	F-ratio	Difference[c]
A. Aiming							
1. Total dots in circles		90.54	120.33	62.14	130.11	19.65[b]	3-4
2. Percentage accuracy 4 trials		76.40	81.44	63.15	86.65	9.50[b]	3-4
B. Time estimation							
1. Time off from 15 seconds		12.28	28.25	34.15	15.58	4.92[a]	4-1
C. Digit Symbol-Unpaced							
1. Correct symbols Trial 2		14.28	16.85	9.86	17.16	19.21[b]	4-3
2. Guess of time to complete test		124.83	140.35	230.76	134.35	9.86[b]	4-1
D. Shift Test							
1. No. 4's crossed over last trial		18.95	21.80	12.81	21.64	18.01[b]	2,1,4-3
E. Digit Symbol-Paced							
1. Percentage accuracy		79.89	86.90	59.23	85.31	7.44[b]	2,4,1-3
F. Gorham Proverbs							
1. Abstract sum		6.37	8.23	4.76	8.00	3.85[a]	2,4,1-3
2. Concrete sum		.79	.57	1.57	.60	7.82[b]	3-1,4,2
3. Abstract plus concrete plus 6		11.08	13.66	8.28	13.40	6.84[b]	2,4,1-3

[a] Significant at .05 level (2-tailed).

[b] Significant at .01 level (2-tailed).

[c] Comma indicates no significant difference; dash indicate significant difference.

Differences between the patients and normals emerged on psychomotor and perceptual tasks in which speed, fine eye-hand coordination, or accuracy were important. In this context it is interesting that the patients performed significantly *better* than the normals on finger tapping under the free condition, i.e., under instructions to tap at a rate that was "comfortable" for them. Hence, they were not deficient in psychomotor performance per se, but deficits did appear when they needed to sustain attention and concentration or where other factors such as energy or motivation were important. As expected, the depressed patients did appear to have more difficulty with the paced digit symbol subtest than with the unpaced version of this test. However, their difficulty was primarily in errors generated and in accuracy which dropped from 95 percent under the unpaced condition to 69 percent under the paced condition. The drop in accuracy for the normal subjects was from 99 to 86 percent which was not nearly as dramatic a drop.

Perceptual flexibility as reflected on Clock Reversal of the Stroop Test and the Shift Test was also an area where there were consistent differences favoring the normal subjects over the patients.

Concrete thinking as measured by the Concrete Sum on the Gorham Proverbs Test was also more prevalent in the depressed sample than in the normals. There were also deficits in the ability of depressed patients to learn nonsense syllables. They not only learned fewer correct symbols but were also more cautious than the normals in guessing at possible correct symbols following the presentation period on the memory drum.

Age-Group Differences

There were 10 significant age-group differences (*see* Table 4). As indicated in the "Difference" column in Table 4, the over-40 patients were most dissimilar from the other groups. They performed slower, with less accuracy, and showed more perceptual rigidity and concreteness in thinking than normal subjects in the same age group. It is also noteworthy that on a number of measures,

normal subjects over 40 did as well or better than the under-40 normals. Hence, although age per se plays some role in psychomotor and cognitive decline, it is the combination of age and depression that seems to have the greatest negative impact on skills in these areas.

Sex-Group Differences

There were only six significant sex-group differences, and in four of these the significant difference was between male patients and male normals. Although the range tests were not significant, the trend in the two other scores was also in the same direction, i.e., with the normal males performing better than the male patients.

Discussion

These results provide compelling evidence that depression does have a negative effect on psychomotor and cognitive skills. The deficits appear to be very general and include tasks requiring sustained effort and concentration, perceptual flexibility or fluidity, abstract thinking, motivation, and accuracy. Simple motor tasks such as finger tapping were not adversely affected by the depression. The results indicate that there is also a tendency for depressed patients to undervalue or deprecate their performance but, in contrast to Friedman's (1964) earlier results, there was some basis in fact for this view, i.e., depressed patients did perform more poorly than their normal counterparts.

The deficits noted in the depressed patients were more pronounced in older patients and the differences were more striking between male patients and male normals than between female patients and female normals. Uhlenhuth (1981) also found a sex difference in the psychomotor performance of depressed patients. He found male depressed patients less efficient than normal men in performing even simple repetitive tasks under various schedules of positive reinforcement. However, depressed women performed more efficiently than their normal counterparts.

There was a general trend in the study for older subjects (patients and normals) to perform poorly on the psychomotor and cognitive tests and for women to perform more poorly than men. Depression tends to magnify these existing age and sex differences but in a somewhat selective fashion. Older depressed patients did more poorly than older normals and male depressed patients performed more poorly than normal males. Dif-

Table 5

Significant Sex-Group Differences on Cognitive and Psychomotor Tests

Variable	Female		Male			
Number	Pt(1) 189	Norm(2) 74	Pt(3) 88	Norm(4) 38	F-ratio	Difference[c]
A. Aiming						
1. No. dots in circles	80.20	119.42	72.48	131.02	5.26[a]	4-3
2. Percentage accuracy for 4 trials	72.60	80.74	66.95	87.35	4.39[a]	4-3
B. Time Estimation						
1. Time off from 15 seconds	-2.12	-4.84	-2.76	-1.67	5.46[a]	
C. Clock Reversal						
1. Combined speed and accuracy score	2.54	3.33	2.43	4.31	4.90[a]	4-3
D. Area Tapping						
1. Speed condition	34.90	44.98	35.24	27.44	8.47[b]	
E. Nonsense Syllable Learning						
1. Syllables attempted	3.66	5.86	3.10	7.63	14.19[b]	4-3

[a] Significant at .05 level (2-tailed).
[b] Significant at .01 level (2-tailed).
[c] Dash indicates significant difference.

ferences were less pronounced between under-40 depressed patients and normals and between female depressed patients and female normals. Hence, it is the patients who are either beginning to experience declines in performance and cognitive skills (older patients) or who have the greatest premorbid strengths in these areas (males) who show the greatest vulnerability to the negative effects of depressive illness.

Although the present study was designed to test a variety of hypotheses related to the effects of depression on psychomotor performance and cognitive skills, this effort was essentially atheoretical. However, study results, particularly the findings that perceptual rigidity and concrete thinking appear to be very prevalent in moderately to severely depressed patients, suggest a possible organic basis for the depression in many of these patients. This is not a new or original thought, but it would be very interesting to select a sample of depressed patients who do poorly on tests such as the Gorham Proverbs and Stroop Color-Naming Test and conduct positron emmission tomography (PET) scans on these patients as has recently been done with schizophrenics.

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Desglycinamide-9-Arginine-8-Vasopressin (DGAVP, Organon 5667) in Cognitively Impaired Patients[1]

Jared R. Tinklenberg, M.D.,[2] Robert Pigache, M.D.,[3] Philip A. Berger, M.D.,[2] and Bert S. Kopell, M.D.[2]

Animal studies and some human trials indicate that vasopressin (VP) peptides can enhance learning and memory in certain conditions (Tinklenberg et al., in press). The following describes a small clinical trial of one VP peptide, desglycinamide-9-arginine-8-vasopressin (DGAVP, Organon 5667), which is of interest because animal studies indicate it is devoid of cardiovascular and antidiuretic hormone (ADH) activity, while retaining behavioral effects (van Riezen 1978).

Method

Eleven men over the age of 50 who had mild to moderate cognitive impairment were studied. They were unable to function occupationally, but could still live independently, did not become disoriented in familiar settings, and showed no marked personality deterioration. The criteria were designed to exclude anyone with severe cognitive limitations or anyone who had always demonstrated low levels of intellectual functioning.

Seven subjects satisfied the Diagnostic and Statistical Manual (DSM-III) requirements for Primary Degenerative Dementia (PDD) (290.10) and met the following additional criteria: insidious onset before age 65 with memory impairment as the initial feature, progressive dementia without stepwise deterioration for at least 2 years before

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[2]Psychiatry Service (116A), Veterans Administration Medical Center, Palo Alto, CA 94304 and Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA 94305.

[3]Scientific Development Group, Organon, International, Oss, The Netherlands.

is study, and a Hachinski score of less than 4. There was no evidence suggesting other causes of ementia, i.e., no cerebral vascular symptoms or gns, hypertension, or other cardiovascular isease, alcoholism, drug abuse, head trauma, pilepsy, or mental retardation. There were no calizing signs on EEG, CT, or neurological ams. X-ray and laboratory exams including 12, T3, T4, and folic acid were normal. There as no indication of significant depression or her psychiatric disturbances on two indepenent exams.

Four patients satisfied the DSM-III requirements for Dementia Associated with Alcoholism (291.22). As with PDD, other causes of dementia were excluded by history, physical, and laboratory exams. There was at least one hospitalization explicitly for alcoholism.

The learning and memory measures, which were chosen on the basis of demonstrated sensitivity to VP or cholinomimetics, were: A 12-word high and low imagery selective reminding learning task and a 20-word delayed free-recall task. To prevent rehearsal between the presentation of the 20 words and their recall 12 minutes later, the subjects were engaged in a distractor task. Behavior and mood were assessed with the Hamilton Depression Scale (Ham-D), Profile of Mood States (POMS), the Sandoz Clinical Assessment -Geriatric (SCAG), and the Nurses Observation Scale for Inpatient Evaluation (NOSIE). The study was conducted at the Stanford Mental Health Clinical Research Center, an inpatient unit at the Palo Alto Veterans Administration Medical Center.

Daily measures of vital parameters and frequent laboratory assessments were also made. After baseline assessments, patients were stratified according to diagnosis and then randomly assigned to one of two parallel groups. Four PDD patients were assigned to the active group and three to placebo. Two alcohol patients were assigned to each treatment group. Each treatment group received placebo DGAVP spray intranasally (i.n.) three times a day (t.i.d.) for 5 days. Then the placebo group continued to receive placebo treatment for 5 more days, whereas the active group received DGAVP 92 μg i.n., t.i.d. (about 202 μg/day free peptide) for the same period. The measures of learning, memory, mood, and general behavior were obtained during baseline, three times during the first treatment period (when both groups received placebo) and three times during the second treatment period.

Results

Preliminary analyses indicated there were no significant differences between the PDD and alcoholic groups, so the two were combined according to which treatment they received. As indicated in the Table, DGAVP did not enhance overall group performance on the two verbal learning measures. Subjects receiving active treatment did remember words with low imagery value better than placebo subjects, but this trend did not reach statistical significance.

Subjects receiving active treatment did improve clinically as indicated by somewhat better scores on the SCAG, but the magnitude of this improvement was small. The Ham-D and POMS-vigor subscale changes suggest the possibility of DGAVP inducing central nervous system stimulation but, again, any such effect was not pronounced. There were no indications of any DGAVP-related side effects and no evidence for pressor or antidiuretic activity.

Comment

The results of this study combined with those of the authors' previous DGAVP study (Tinklenberg et al. 1982) indicate that any effects of this dosage schedule may be too small to be of clinical significance. Since the few patients who did improve during the active treatment period generally had higher scores on initial measures of depression, the possibility of this VP peptide inducing mild mood elevation should be considered, especially since other VP peptides may ameliorate certain forms of depression (Gold et al. 1979). The failure of PDD patients to respond significantly to DGAVP in this study is consistent with unimpressive findings in two earlier studies of related VP peptides lysine-vasopressin and desamino-8-D-arginine vasopressin (DDAVP) in PDD patients (Chase et al. 1982; Tamminga et al. 1981; Tinklenberg et al. 1982). However, these unconvincing results are in contrast to the recent positive treatment of very early PDD pa-

Table

		Mean of First Treatment Period (Placebo/Placebo)	Mean of Second Treatment Period (DDAVP/Placebo)	Standard Error of Difference
12-Word Selective Reminding Learning Total Recall	Active Group ($N = 6$)	8.56	8.78	
	Placebo Group ($N = 5$)	7.0	7.4	0.35
20-Word Delayed Free Recall	Active Group	2.22	2.22	
	Placebo Group	2.93	3.73	0.93
Sandoz Clinical Assessment Geriatric (SCAG)[a]	Active Group	40.6	37.6	
	Placebo Group	31.9	31.6	0.99
Hamilton Depression (Ham-D)[a]	Active Group	8.2	7.8	
	Placebo Group	2.1	2.3	1.45
Profile of Mood States (POMS): Vigor	Active Group	55.0	60.6	
	Placebo Group	56.0	55.75	4.03

[a] Lower score indicates improvement

tients with DDAVP (Weingartner 1981). Further studies of these interesting peptides using more extensive dosage schedules and larger numbers of patients are being conducted to resolve these apparent discrepancies.

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How Does Methylphenidate (MP) Affect Information Processing in Man?

Enoch Callaway, M.D.[1] Roy Halliday, Ph.D.,[1] Shirley Peeke, Ph.D.,[1] and Victor Reus, M.D.[1]

The purpose of this paper is to argue that methylphenidate (MP) and probably other short-acting stimulants act on response-related processes at the output end of information flow and that they have little effect on input function such as stimulus evaluation.

The latency of the P3 component in the average evoked potential appears to reflect time spent evaluating the stimulus. For example, degrading the quality of a stimulus slows both reaction time and P3. Response factors such as response competition, response readiness, and response complexity influence reaction time as do stimulus related factors. However, in contrast to stimulus related factors, these response related factors do not influence P3 latency (McCarthy & Donchin 1981).

The authors found that MP speeded reaction time in a group of older hyperactive children but had no effect on the latency of the visual evoked potential P3 component. By contrast, when the comparisons were made between children, reaction time and the P3 latency were strongly related. Apparently the changes due to maturation and P3 latency influenced both reaction time and P3 latency, while changes induced by MP only affected reaction time and did not affect P3. This is illustrated in the Figure. Thus, maturation seems to speed stimulus evaluation, since it speeds both P3 latency and reaction time. MP seems to speed reaction time without influencing stimulus evaluation as indicated by P3 latency.

Another study of hyperactive children done in this laboratory also suggested that MP is not effective in altering perceptual processes. In this study moderate doses of MP improved memory performance. By contrast, MP had no effect on a span of apprehension test. This latter task requires searching a tachistoscopically projected array for a hidden item. Presumably, performance on this task is a function of speed in perceptual processing.

The fact that P3 latency reflects stimulus evaluation and methylphenidate does not affect P3 latency is further illustrated in another study from this laboratory. This one involved eight women between the ages of 30 and 40. A test was designed to include two levels of stimulus complexity and two levels of response complexity that could be combined to provide four difference tasks. The easy stimulus was an "X" that appeared in any one of four possible horizontal positions. The hard stimuli consisted of the "X" target with three stars which occupied the other three positions. Easy response consisted of pressing one key every time an X appeared. The hard response consisted of pressing one of four keys depending on the horizontal location of the target.

Reaction times and latencies of P3 were collected for all four tasks both before and 45 minutes after taking a pill. The pill contained either a placebo or MP in doses of 5, 10, or 20 mg.

MP speeded RT for all tasks but did not change P3 latency. Increasing both stimulus complexity and response complexity showed reaction time. The increase of stimulus complexity also increased P3 latency, but response complexity did not. Thus, MP acts after the processes involved in stimulus evaluation have been completed.

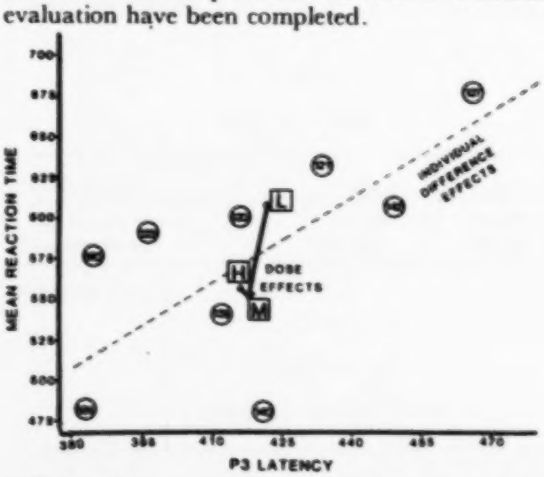

FIGURE: Effects of MP and maturation on reaction time and P3 latency. 0 = average across doses of MP for individual subjects. Figure in circle is age in months. / / = average across subjects for each dose. L = Low .16 mg/kg. M = Medium .33 mg/kg. H = High .66 mg/kg.

[1]Langley Porter Psychiatric Institute, University of California, San Francisco Medical Center, San Francisco, CA 94143.

The notion that MP speeds response-related operations is consistent with reports in the literature. For example, Mohs et al. (1978) presented rows of print that were to be scanned for a single character and reported that a short-acting stimulant speeded this ordered search. Frowein (1981) has reported that amphetamine did not react with stimulus variables in a series of tasks where varying degrees of stimulus response complexity were combined. However, it did speed the motor response component of this task.

To summarize, then, the available data suggest that MP and perhaps other stimulants do not influence stimulus evaluation processes, but rather act on the performance end of the stimulus/response arc.

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Parental Reports of Adverse Responses to Food Substances in Child Psychiatry Patients and Normal Controls

Jovan G. Simeon, M.D.,[1,2] H. Bruce Ferguson, Ph.D.,[1,3] Carole Anne Ralph,[1] and D. Mistry, M.D.[1]

Adverse responses to food substances have long been implicated as etiological factors of hyperactivity, conduct problems, and learning disorders in children. Most of the claims in the older literature associating food substances and behavior disorders are based on poor scientific methodology and anecdotal reports. An important drawback in research regarding allergic reactions has been the lack of reliable and valid diagnostic tests and criteria for allergies. Nevertheless, in the past decade, the popularity of this general approach has grown and publications advocating special diets for children with hyperkinetic and learning disorders have proliferated in North America. Such dietary management has been reported to result in relief of chronic disabling mental and physical symptoms (Crook 1980; Feingold 1975; Rapp 1979).

Controlled research studies examining hypotheses of detrimental effects of general food allergies (Trites et al. 1980) or adverse responses (of an unknown nature) to dyes and additives (Conners 1980; Goyette et al. 1978; Harley et al. 1978) have reported generally negative findings. There seems to be some agreement that a small proportion of children, perhaps the younger ones, are affected adversely by these latter substances. However, this conclusion leaves the clinician in a difficult position until valid and reliable diagnostic tests are evolved. To obtain a different perspective on the seriousness of the problem of adverse responses to food substances for child psychiatry, the authors compared parental reports

[1]The Royal Ottawa Hospital, Ottawa, Canada.
[2]Department of Psychiatry, School of Medicine, University of Ottawa, Ottawa, Canada.
[3]Department of Psychology, Carleton University, Ottawa, Canada.

Note: Copies of the questionnaires may be obtained by request from: Jovan G. Simeon, M.D., The Royal Ottawa Hospital, 1145 Carling Avenue, Ottawa, Canada K1Z 7K4.

of such responses in a psychiatric sample with those of a control sample of unscreened school children. Their research hypothesis was that if adverse responses to food substances were an important etiological contributor to psychiatric problems in children, then parental reports of a referral sample ought to reveal a higher frequency of such associations than parental reports from a control sample.

Method

Psychiatric Referral Sample

Two hundred "active" files were selected from the records of the Children's Outpatient Psychiatric Department, Royal Ottawa Hospital. Current addresses were available for 190 of these children and questionnaires regarding any adverse responses to food substances and allergies were mailed out with stamped, return envelopes.

Control Sample

Permission was obtained from the Ottawa Board of Education to distribute questionnaires to elementary school students. Five hundred children, approximately evenly distributed through Grades 1 - 6 (age – 6.5-11.5) were given cover letters and questionnaires with stamped, return envelopes. All these children were in two schools chosen in consultation with Board officials to represent a broad range of socioeconomic status variables.

Questionnaires also obtained information about the child's age and sex, sibling sex and age, medical and academic problems, and allergic responses among family members.

Table 1

Number (and Percent) of Questionnaires Returned by Group

	Sent Out	Returned	Percent Returned
Psychiatric Group	190	57	30.0
Control Group	500	192	38.4

$X^2 = 3.88\ p < .05$

Results

Response Rate

The response rate of the control sample was significantly higher than that of the psychiatric group (*see* Table 1).

Age Characteristics of Groups

The age range of the psychiatric group was 6-18 years with only 8 of 57 returned forms for children over 13. Those returning questionnaires in the school group had an age range of 5-13 years with relatively few children aged 5, 12, or 13. For the purpose of group comparison, age was divided into "young"(5-8 years inclusive) and "old"(9+ years) categories. The significant chi-square (*see* Table 2) reflects the preponderance of the psychiatric group in the "old" category, while the control sample was evenly split with regard to age.

Sex

There were relatively more males in the psychiatric group. This difference was significant (*see* Table 3) and is consistent with the generally accepted preponderance of boys in child psychiatric populations.

Table 2

Age by Group

Number (percent)	Young	Old
Psychiatric Group	14 (25)	43 (75)
Control Group	93 (48)	99 (52)

$X^2 = 9.28\ p < .01$

Table 3

Sex of Group

Number (percent)	Male	Female
Psychiatric Group	44 (77)	13 (23)
Control Group	90 (47)	102 (53)

$X^2 = 15.09\ p < .01$

Reported Adverse Responses or Allergies

Frequency of reported allergies was first examined collapsing across age and sex. The categories examined were: a) reaction only to foods; b) reaction to foods plus has allergies to other substances; and c) reaction to foods or has allergy to other substance. Although the rate of reported reactions was higher for the psychiatric group, there were no significant differences between groups (chi-square). Expressing the frequency of adverse responses to food as a proportion of all reported adverse effects (psychiatric group: 17/28-61 percent; control group: 39/79-49 percent) again revealed no significant difference between the groups.

Adverse Responses or Allergies: Group × Sex: Separate 2 × 2 comparisons of the groups for each sex showed no significant differences, despite the increased difference between groups for males on some variables (*see* Table 4). In addition, there was no difference between groups on adverse responses to foods expressed as a proportion of other allergies.

Table 4

Type of Adverse Response/Allergy as a Function of Group and Sex

Number (percent)	Psychiatric Group		Control Group	
	Male (*N* = 44)	Female (*N* = 13)	Male (*N* = 90)	Female (*N* = 102)
Reacts to food only	5 (11)	0 (0)	8 (9)	15 (15)
Reacts to food *plus* other	14 (32)	3 (23)	17 (18)	22 (22)
Reacts to other only	3 (7)	3 (23)	12 (13)	5 (5)
Reacts to food *or* other	22 (50)	6 (46)	37 (40)	42 (41)

Adverse Responses or Allergies: Group × Age: Although some of the psychiatric group values appeared higher for "young" subjects (*see* Table 5), the small number of psychiatric group children in this category make these figures unreliable. Once again, separate 2 × 2 chi-square comparisons of the groups for each age category showed no difference on any variable. In addition, there was no difference for adverse responses to food expressed as a proportion of other allergies.

Table 5

Type of Adverse Response/Allergy as a Function of Group and Age

Number (percent)	Psychiatric Group		Control Group	
	Young (*N* = 14)	Old (*N* = 43)	Young (*N* = 93)	Old (*N* = [illegible])
Reacts to food only	2 (14)	3 (7)	15 (16)	8 (8)
Reacts to food *plus* other	5 (36)	12 (28)	18 (19)	21 (21)
Reacts to other food	1 (7)	4 (9)	2 (2)	15 (15)
Reacts to food *or* other	8 (57)	19 (44)	35 (38)	44 (44)

Type of Symptom Shown to Food Substances

Symptoms were divided into three categories: a) physical symptoms, e.g., nausea; b) behavioral symptoms, e.g., hyperactivity, irritability; c) both physical and behavioral. In addition, the behavioral and "both" categories were combined to give a "total behavioral" symptoms category. The small numbers involved made it necessary to carry out this analysis collapsed across age and sex. Again, though the psychiatric group rates were higher for some variables (both, total behavioral), there were no statistically significant differences.

Substances Causing Symptoms

Both groups were sensitive to the same substances, both food and non-food. An exception was the high incidence of problems of the psychiatric group with pollens (15 vs. 4). Another point of note is that "sweets" (sugar plus chocolate) were reported to cause problems for twice as many children as food dyes or additives (25 vs. 11).

Role of Adverse Responses in Problems

Since the psychiatric group by definition had all been referred for emotional/behavioral/school problems, the role of adverse responses in producing medical, emotional, and school problems was examined in the school group (*see* Table 6).

Chi-square comparisons showed that the "food plus" group had significantly more medical and emotional problems than the "other" or "none" groups and that the "food plus" group had significantly more school problems than the "none" group only ($p < .05$). Thus, it appears that such reports of adverse responses to foods and other substances may indeed be related to incidence of such problems.

Table 6

Type of Adverse Response in the School Group

Number (percent) Adverse Response to:	Problem Area Medical	Emotional	School
Food only ($N = 21$)	6 (29)	1 (5)	5 (24)
Food plus other ($N = 15$)	10 (67)	5 (33)	7 (47)
Other ($N = 41$)	13 (32)	3 (7)	8 (20)
None ($N = 102$)	17 (17)	7 (7)	18 (18)

Relation to Family Problems with Allergies

Only one psychiatric subject had a family member with adverse responses to food, while seven school subjects had family members with such responses. All eight of these children had adverse responses to foods. No family of a child without adverse responses reported a family member with an adverse response to a food substance.

The incidence of reported "allergies" among family members was higher among families of children reported to have adverse responses or allergies (78 vs. 53 percent). Whether or not the child showed adverse responses, the incidence of allergies reported for family members is about 10 percent higher in the school sample. However, chi-square analysis indicated that there were no significant differences between the psychiatric and school groups among subjects either with or without adverse responses.

Conclusion

The most noteworthy finding was the similarity between psychiatric and school groups in frequency and type of adverse responses and the substances to which they were reported to respond. While the problems appeared to be relatively more marked for boys and "young" subjects in the psychiatric sample, these differences did not reach significance. However, some care must be exercised in interpreting these results. Neither sample produced a satisfactory response rate and the school group's response rate was higher than the psychiatric group's. This low response rate leaves open the possibility that real differences in the populations are masked by some unknown sampling bias. Finally, the data showing that children in the school group with adverse responses to food and other substances were reported to have more problems than other children suggests that such adverse responses may indeed play some role in producing physical, behavioral, and school problems.

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Classical Conditioning of Cocaine's Stimulatory Effects

Wagner H. Bridger, M.D.,[1] Stanley R. Schiff, M.D.,[1] Stanley S. Cooper, M.D.,[1] William Paredes, M.D.,[2] and Gordon A. Barr, M.D.[1]

The ability of environmental cues that become associated with drug administration to elicit behaviors originally due to the drug alone is well established. Pavlov (in 1927) first suggested that cues paired with drug treatment could be viewed as conditioned stimuli within the framework of classical conditioning.

However, although conditioning of opiates effects is now well accepted, the ability of conditioned stimuli to elicit stimulant-like behavior is not as established. (Irwin & Armstrong 1961; Pickins & Crowder 1967; Pickens & Dougherty 1973; Pilil & Altman 1971; Schiff, in press; Segal 1975; Tilson & Rech 1973). More recently, Post and his colleagues have argued that conditioned stimuli alone are not able to elicit increased activity and stereotypic behaviors typical of cocaine (Post & Rose 1976; Post et al. 1981). On the other hand, stimuli associated with reinforcing intravenous infusions of cocaine act as "priming" doses to facilitate responding for cocaine during extinction (deWit & Stewart 1981).

In the present series of experiments, the following questions were asked: 1) Can stereotyped behavior and hyperactivity elicited by cocaine be classically conditioned? 2) For how long can the conditioned stimuli continue to elicit cocaine-like behaviors with and without extinction?

Experiment I

Male Long-Evans hooded rats from Blue Spruce Farms (Altamont, N.Y.) aged about 90 days, were used. Two groups of rats, conditioned and pseudoconditioned controls, were used for all experiments. Both groups were given training trials in which they were placed into a 10-gallon glass aquarium for 1 minute during which time a tone which served as a conditioned stimulus was presented (2800 Hz Sonalert). Following this, the rats were injected with either 15.0 mg/kg cocaine HCL (Malincrodt) or 0.9 percent saline (1ml/kg) and placed into the second aquarium in a separate room. This procedure was done on 10 consecutive days. On the test day the procedures were identical except that all animals were injected with saline. After each training session, animals were returned to their home cages where they received, approximately 1 hour later, an injection of the opposite drug or vehicle. This served to equate the amount of cocaine received by both groups.

Seven separate behaviors were measured by an experienced rater blind to the experimental conditions through a one-way mirror from a separate room. These behaviors have been defined previously (Schiff, in press). Separate behaviors were measured rather than combining them into a single "stereotypy" score, because most stereotypy scales are defined to be linear and interval scales rather than being empirically derived as such. Thus, they are examples of what Torgerson (1967) calls measurement by fiat. Second, the authors and others (Costall & Naylor 1980; Eichler et al. 1980; Iverson 1977; Schiff 1980) reported that individual stereotyped behaviors may be mediated by different physiological systems.

Because there existed some question about the ability of conditioned stimuli to elicit increased activity and stereotypy, the initial experiment was designed to determine if, using the authors' methods, conditioned cocaine-like effects could be demonstrated.

Results

The conditioned group was compared to the pseudoconditioned group for each behavior by independent *t*-tests. These data are presented in the first table. Seven of the eight behaviors showed significant differences between groups, with licking not being conditioned.

Experiment II

It was established in the first experiment that seven of eight behaviors elicited by cocaine could

[1]Department of Psychiatry, Albert Einstein College of Medicine, Bronx, NY 10461.
[2]Department of Psychology, Hunter College, City University of New York, New York, NY 10021.

be conditioned. Yet, for these findings to have practical significance it is necessary, although not sufficient, to demonstrate that the conditioned effect has some permanence. In this second experiment, we delayed testing the animals with saline for 5 days to see if the conditioned effect would last that long. Since it did, we tested twice more at 5-day intervals.

The methods were similar to those in the first experiment except that the initial test day was 5 days after the 10th training day rather than 1 day. Subsequent test days (saline injections) were 10 and 15 days posttraining.

Results

The data were analyzed by a two-way analysis of variance (Group × Day of testing) with particular attention paid to the interaction term. First, licking, grooming, and chewing did not show significant differences between groups and also failed to show significant interactions ($p < .05$). This suggests that the conditioned drug effects were dissipated by the first day of testing, Day 5, for these two behaviors; licking failed to show conditioning in Experiment 1. Sniffing and head-bobbing both demonstrated significant

Table 1

Behaviors Elicited by the CS for Conditioned and Pseudoconditioned Groups

	Licking	Head Bobbing	Chewing	Sniffing	Grooming	Rearing Time	Crossing	Rearing Frequency
Condit.	.29	91.37[a]	2.41[b]	99.75[b]	15.65[a]	33.81[b]	10.78[b]	8.27[b]
	.14	5.22	0.88	4.32	3.79	4.60	1.04	1.10
Pseud Condit.	.26	52.04	5.81	62.31	28.51	14.11	5.36	4.03
	.13	5.97	1.39	6.55	4.57	2.86	1.01	.71

[a] $p < .05$

[b] $p < .01$

Note- Entries are Means and Standard Errors of the Mean in seconds/ 120 second period except for crossings and rearing frequencies which are number/ 120 second period. Statistical significance was tested with independent *t*-tests. $N = 16$/ group.

Table 2

Differences Between Conditioned and Unconditioned Groups to the CS 5, 10, and 15 Days Posttraining

	Day	Licking	Head Bobbing	Chewing	Sniffing	Grooming	Rearing Time	Rearing Frequency	Crossing
Condit. Group	5	0.97	65.76	1.91	85.02	21.05	26.87	6.29	10.79
		0.45	4.51	1.20	5.57	7.47	5.02	1.03	1.61
	10	0.52	67.55	0.90	87.08	15.81	20.39	6.38	10.71
	15	1.60	54.61	1.99	80.06	16.04	16.29	6.66	9.33
		0.72	3.47	0.75	4.69	4.07	3.10	0.76	1.16
Pseudo-Condit. Group	5	2.56	33.51	5.27	45.98	27.12	11.98	3.25	4.04
		0.97	4.26	2.20	5.15	6.92	3.88	0.81	0.91
	10	2.40	27.79	2.89	43.15	28.28	9.17	2.46	2.92
		1.13	6.29	1.39	9.08	7.49	3.59	0.84	1.06
	15	3.22	41.64	4.48	63.01	22.39	15.45	4.16	5.91
		0.78	5.29	1.64	5.79	8.11	4.15	0.94	0.82

Note- Entries are Means and Standard Errors of the Mean in seconds/120 second period except for crossings and rearing frequencies which are numbers/120 second period. For statistics see text. $N = 8$/group.

group effects ($p < .001$) and significant interactions ($p < .05$). Subsequent analysis of the interactions by tests of simple main effects (Kirk 1968) showed that there were significant differences between groups on Days 5 and 10 but not on Day 15. Finally, the number of crossings and the frequency of rearing showed significant group differences but failed to show significant interactions (although there was a trend for a significant interaction for crossing, $p < .09$). This suggests that any decay for these two behaviors over the 15 days was minimal. The data are presented in Table 2.

Experiment III

In part because the second experiment which studied decay of the conditioned response contained an extinction component, and in part to determine if the conditioned effect could be decreased by extinction, the conditioned stimuli was presented without the unconditioned stimulus for 4 consecutive days. The ability or inability to extinguish the conditioned response could have implications for the treatment of stimulant abusers. The methods were identical to those of the second experiment, except that there were 4 consecutive test days beginning with Day 11.

Results

Data were analyzed in an identical manner to those in the second experiment. An analysis of variance was done on the data with a significant interaction indicating differential changes in the two groups over the 4 days of testing. This analysis failed to show significant differences between the conditioned and pseudo-conditioned groups for licking, chewing, or grooming. For licking this was a replication of the failure of this behavior to condition, but for the latter two behaviors it indicates caution in concluding that these two behaviors reliably condition. Rearing time only showed a trend towards conditioning ($p < .07$) and the comments above also apply here. Rearing frequency, crossings, sniffing, and head bobbing all showed significant group differences ($p < .05$, $< .01$, $< .001$, $< .05$, respectively) but no behavior showed any significant interactions or trends towards significant interactions ($p < .10$). Again, while nonsignificant differences must be interpreted with caution, this suggests that these behaviors did not show major extinction during the 4 extinction days. Table 3 presents the data.

Table 3

Differences Between Conditioned and Unconditioned Groups to the CS During 4 Days of Extinction

	Day	Licking	Head Bobbing	Chewing	Sniffing	Grooming	Rearing Time	Rearing Frequency	Crossing
	1	0.72	51.80	1.06	72.30	27.04	19.24	5.33	6.92
Condit.		0.28	4.07	0.31	2.97	8.81	4.01	0.84	0.85
Group	2	1.15	47.05	2.31	64.92	27.86	13.67	4.62	6.08
		0.75	6.54	1.09	8.72	6.67	3.46	1.22	1.86
	3	0.84	48.56	1.64	61.62	27.32	17.08	5.88	8.21
		0.32	6.95	0.47	8.55	6.84	2.19	0.80	1.12
	4	1.18	36.13	2.15	52.18	25.30	11.19	3.79	5.21
		0.56	10.74	1.08	11.14	992	5.20	1.69	1.99
	1	1.40	35.23	4.08	53.60	23.47	9.07	2.29	3.66
Pseudo-		0.62	5.34	1.55	7.26	8.57	2.59	0.79	0.54
Condit.	2	0.97	37.73	4.22	49.65	17.17	8.36	2.41	3.71
Group		0.48	6.94	2.13	8.99	6.58	3.77	0.96	0.86
	3	1.25	24.80	2.05	32.18	36.15	6.58	2.04	2.75
		0.38	4.74	0.55	6.22	4.54	2.66	0.76	0.84
	4	1.18	26.58	8.38	34.09	35.83	7.71	1.92	3.83
		0.52	5.86	0.21	5.55	8.28	3.40	0.68	0.97

Note- Entries are Means and Standard Errors of the Mean (see Table 1). N = 8/group.

Discussion

The results of these experiments demonstrate that cocaine-like behaviors can be readily elicited by previously neutral stimuli that had been paired with cocaine and that these effects, for some of the behaviors, are stable over time.

The differences between the results found here and those of Post and his colleagues are likely due to one of two major methodological differences (Post & Rose 1976; Post et al. 1981). Conditioned stimuli were presented for the experimental group only with cocaine. In contrast, the National Institute of Mental Health (NIMH) group allowed 20 minutes of adaptation to the test chamber prior to drug injection. Thus, along with each conditioning trial was an extinction period. Others have reported relatively rapid extinction of the enhancement of cocaine's effects by conditioned stimuli (Hinson & Poulos 1981). Moreover, the authors attempted to increase the likelihood of conditioning by having multiple conditioned stimuli such as tone, injection, novel chamber, and removal to the observation room. It is likely that the conditioned drug effect requires these multiple cues.

A second procedural difference is the dependent measure. We examined individual behaviors and found that not all conditioned with equal ease. Most other investigators have used rating scales that combine behaviors. That some behaviors show more conditioning than others supports the argument that the different behavioral components of stereotyped behaviors may have different anatomical or chemical substrates.

These data have implications for the etiology and treatment of drug-seeking behavior. There are two ways in which environmental stimuli can affect stimulant abuse. The first is the enhancement of stimulant action by association with environmental cues (Hinson & Poulos 1981; Post & Rose 1976; Post et al. 1981; Segal & Mandell 1974). This may contribute substantially to resultant drug actions, including hyperactivity, stereotypy, and convulsions (Post et al. 1981). However, an equally important component is the role of these same environmental cues in the absence of drug. These cues can result in behavioral and presumably physiological effects that mimic the stimulant. In as much as "priming" doses of drug can lead to drug-seeking behavior in animals (Davis & Smith 1976; deWit & Stewart 1981; Gerber & Stretch 1975; Pickens & Harris 1968), stimuli associated with drug intake in a Pavlovian manner can also do the same (deWit & Stewart 1981). For opiates, the role of these stimuli in recidivism has been recognized. The authors suggest that similar processes may be functioning for stimulant abuse.

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Naloxone Potentiates Cocaine Effect in Man

Robert Byck, M.D.,[1,3] Alan Ruskis, M.D.,[2] James Ungerer,[3] and Peter Jatlow, M.D.[3,4]

The effects of cocaine on mood and physiological parameters in man are well established. Naloxone (an opioid antagonist) has minimal mood and cardiovascular effects. The proposal for a common mechanism of euphoria mediated by endorphins (Byck 1976) would imply a possible block of cocaine euphorigenic effects by naloxone. Similar reasoning by Huey et al.(1980) led to an experiment examining the effects of naloxone on methylphenidate-induced mood enhancement. No block was found, but some effects of methylphenidate appeared to be enhanced, although not at a statistically significant level.

The authors examined the effects of 20 mg IV naloxone on mood and physiological parameters on seven male volunteers who had received 2 mg/kg cocaine intranasally. Cocaine effects in the predictable directions occurred, but naloxone given at 15 minutes after cocaine enhanced rather than blocked cocaine "high;" there was an increase in "euphoria" and a depression of "lethargy," "malaise," and other psychological measures consistent with enhanced cocaine effect. The effect on physiological parameters was variable. When naloxone was given at 5 minutes before cocaine or 25 minutes after cocaine, no significant changes in cocaine effects were seen.

Holaday and others (Faden et al. 1981) have reported naloxone reversal of endotoxin and spinal shock by a postulated central dopaminergic mechanism. The authors suspect that their observed potentiation of cocaine effect occurs by a similar dopaminergic mechanism and that administration of cocaine or methylphenidate "sets up" a dopamine agonist response to naloxone similar to that caused by shock-inducing mechanisms.

The apparent necessity for naloxone dosage to follow cocaine rather than precede it implies a

[1]Departments of Pharmacology, [2]Anesthesiology, [3]Psychiatry, and [4]Laboratory Medicine, Yale University School of Medicine, New Haven, CT 06510.

cocaine effect on a naloxone sensitive system which may not be a traditional opiate receptor mechanism. Since naloxone effects are, if anything, the reverse of cocaine effects, the finding of a potentiation is clearly more than an additive interaction.

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Rapid Acquisition of Conditioned Responses to Hydromorphone in Detoxified Heroin Addicts

Joseph W. Temes, Ph.D.,[1] Charles P. O'Brien, M.D., Ph.D.,[1] and Thomas T. Testa, Ph.D.[1]

A Pavlovian conditioning procedure was used to study conditioned drug states in human subjects. Six recently detoxified heroin addicts received six training trials in which two arbitrarily selected stimuli, a strawberry-flavored solution and a 700 Hertz (Hz) tone, were used to signal an infusion of 4 mg of hydromorphone.

Subjects' verbal reports of craving, withdrawal, and high, and two autonomic variables, skin temperature and pupil diameters, were recorded to assess the effects of this training. The unconditioned response to hydromorphone included an increase in skin temperature, pupilary constriction, reports of feeling high, and a reduction in craving and withdrawal symptoms. During *training* with hydromorphone, the conditioned stimulus (CS) elicited a mixed anticipatory response pattern. It partially resembled the unconditioned drug reaction, since the subjects reported feeling high and had fewer withdrawal symptoms. On the other hand, it partially resembled unconditioned withdrawal since they also reported an increase in craving, their pupils became dilated, and their skin temperature decreased. During *test* trials, when physiological saline was substituted for hydromorphone, both the subjective reports and autonomic variables changed in the opposite direction from the drug's unconditioned effects. Additionally, subjects displayed extreme negative affect 15 to 20 minutes after the saline infusion. The authors believe this is the phenomemon which is commonly referred to as "conditioned withdrawal."

Classical conditioning readily occurs when opiate drugs are used as unconditioned stimuli (UCSs). Thompson and Pickens (1971) demonstrated that a drug-produced state can act as an interoceptive stimulus in control of operant

[1]Department of Psychiatry, University of Pennsylvania and Veterans Administration Medical Center, Philadelphia, PA 19104.

behaviors. Wikler (1973) observed that opiate drugs elicit compensatory physiological changes which are conditioned responses CRs. Recently Siegel (1976) demonstrated that tolerance to morphine in rats is a Pavlovian CR. Conditioning can also produce an interoceptive state which resembles abstinence symptoms and which motivates opiate-seeking behavior in detoxified addicts (Goldberg & Schuster 1970). This latter CR is sometimes called "conditioned withdrawal" (Wikler 1965).

The evidence for the phenomenon known as "conditioned withdrawal" is still somewhat speculative. Teasdale (1973) found that showing slides of drug-related scenes to post-addicts resulted in significant changes in mood. O'Brien et al. (1977) reported that conditioned abstinence symptoms were produced by pairing a tone/odor CS with naloxone injection in methadone addicts. Ternes et al. (1979) and Hugdal and Ternes (1981) have shown that naturalistic stimuli such as syringes, bags of heroin, and video sequences of self-injection were capable of eliciting electrodermal arousal and autonomic changes similar to opiate withdrawal signs in detoxified addicts. Ternes and O'Brien (1982) have also reported that when detoxified addicts were allowed to self-inject saline, autonomic changes occurred which were in opposition to the usual effects of an opiate. They argue that the syringe and self-injection procedure are naturally conditioned CSs which elicit anticipatory CRs which resemble withdrawal signs. These CRs may also be correlates of a conditioned emotional state which motivates behavior as a means of avoiding abstinence syndrome. However, to date no clear demonstration of how conditioned withdrawal responses are acquired in human subjects has been published.

The Laboratory at the Veterans Administration Drug Research center in Philadelphia has been engaged in studying the role of Pavlovian conditioned responses in human opiate addiction for the last 10 years. In earlier works, the authors have attempted to demonstrate experimental extinction of naturalistic stimuli normally associated with heroin self-administration (O'Brien et al. 1979). It could be argued, however, that what appeared to be conditioned reactions to stimuli normally associated with self-injection were in fact unconditioned arousal responses and movement artifacts which were unconditionally elicited by the syringe and the act of self-injection. The present experiment controlled for these possibilities. This was accomplished by pairing entirely arbitrary stimuli, a strawberry flavor and a 700 Hz tone, with a 4 mg dose of hydromorphone delivered within a 30-second interval as a 2 ml bolus of solution superimposed on the slow infusion of 5 percent dextrose and water which was administered throughout the session. The infusions were administered through an intravenous catheter which was inserted in the median cubital vein prior to each session. The authors believe this procedure is free from the contaminating influences of the subject's prior history of associations with self-injection. It should also be relatively free from the unconditioned arousal effects of the injection stimuli, from movements during drug administration and, finally, from the necessity to use a tourniquet.

Method

Subjects

The subjects were six male heroin addicts with a mean history of heroin use of 5.7 years. Each patient was required to detoxify completely and remain drug-free for 2 days following the last methadone dose. All subjects signed a consent form and became an inpatient on the detoxification ward at the Veterans Administration Medical Center in Philadelphia.

Apparatus

An intermittent infusion set delivered either the UCS or a placebo and was placed in the arm of the subject prior to the beginning of each test session. The administration set was connected to polyethylene tubing which was passed through an aperture in the wall to an adjoining room where it was attached to a Harvard infusion pump.

Procedure

There were 10 daily experimental sessions. Prior to each of these, the subject was prepared for physiological recordings by attaching a thermister to the right index finger. Each session was

60 minutes long. Prerecorded instructions asked the subject to rate his level of craving, high, and withdrawal in order to assess his subjective state at various points throughout the session. He was also asked to drink a flavored liquid when he heard a tone onset. The first 10 minutes of the session were silent except for the verbal self-reports which occurred at 5-minute intervals throughout the session. This constituted the session baseline period. Tone onset (65 db, 700 Hz audiogenerator) occurred at the end of this baseline period. At that time, the patient was also instructed to drink 70 ml of strawberry Hawaiian punch. The tone as well as the highly salient strawberry taste constituted a complex CS for the delivery of the drug. At the end of the 4th minute of the tone, the infusion pump was turned on. On the first 2 days (pretraining), as well as on the last 2 days (testing), physiological saline was infused instead of hydromorphone. During Sessions 3 through 8 (training), 4 mg of hydromorphone was infused. Delivery of the solution on both drug and placebo days was accomplished by a 4 cc syringe attached to a Harvard infusion pump. This was followed by a flush of 5 cc of 5 percent dextrose and water from a second 5 cc syringe, also placed in the pump. At this point, the subject was given the same set of questions. The questions were repeated at 10-minute intervals until the end of the session at minute 60.

The autonomic measures taken from all patients during the 60-minute session were: pupil size and skin temperature. Subjective reports of high, craving, and withdrawal were also elicited from the subjects by requesting a response from fixed choice questions such as: "Do you feel any high, craving, withdrawal/none, mild, moderate, extreme?"

Results

Figure 1 shows the mean change in subjective reports by the subjects after the CS was presented during each of the three conditions of the experiment: pretraining baseline, training with hydromorphone, and testing with saline. During pretraining sessions there were only slight changes in the subject's reports of craving, high, and withdrawal. When the CS was presented during *training*, craving and high increased and withdrawal decreased relative to the severity of these reports during the session baseline period. During *testing*, both craving and withdrawal increased but no reports of feeling high occurred. These results suggest that conditioned high responses were acquired during training with hydromorphone and that these CRs were accompanied by increased levels of craving and decreased withdrawal. However, when a placebo was given, subjective reports of craving were followed in time by withdrawal symptoms.

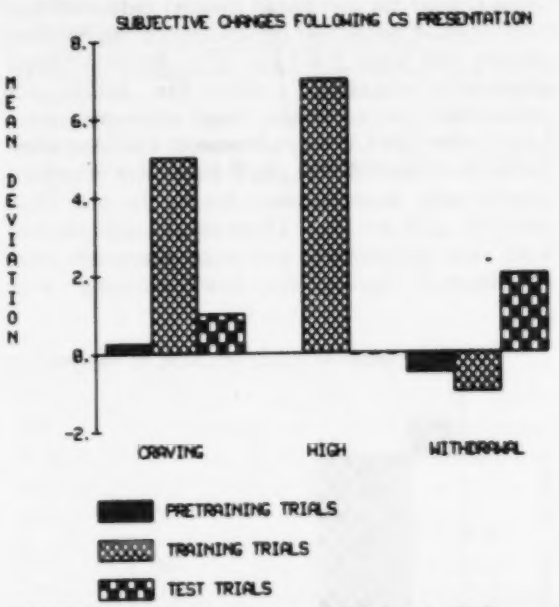

FIGURE 1. Subjective Changes Following the CS Presentation. Craving, high, and withdrawal expressed as mean deviations from session baselines across three experimental conditions: pretraining, training, and testing. Each mean is based on two trials. The filled bar is the mean of the pretraining trials (Trials 1 and 2). The crosshatched bar is the mean of the last two training trials (Trials 7 and 8). The checkered bar is the mean of the two test trials (Trials 9 and 10).

Figures 2 and 3 show the mean deviations in skin temperature and pupil diameters from session baseline which were elicited by the CS presentation during the pretraining, training, and test phases of the experiment. A slight positive change in skin temperature occurred during the pretraining trials. During training and testing, however, all of the changes in skin temperature were in a negative direction relative to the respective session baseline. Pupil diameters decreased

slightly during the pretraining trials. During training and testing, all of the changes in pupil diameter were positive relative to the session baselines.

In the presence of CF, both of these autonomic variables changed in the opposite direction from the unconditioned response to hydromorphone. During training, skin temperature increased after the UCS presentation. On test trials when no drug was given, skin temperature decreased following the CS presentation. Planned comparisons (*t*-tests for correlated means) indicated that temperature decreased significantly from baseline during test trials ($t=3.25$, df 5, $p<.01$). Pupil diameters decreased after the UCS was presented. On test trials, pupil diameters were larger after the CS was presented. Planned comparisons indicated that pupil diameters increased significantly from baseline during the test trials ($t=2.83$, df 5, $p<.01$). These results indicate that both skin temperature and pupil diameters were conditioned during the brief training with hydromorphone. These results also indicate that these autonomic CRs resemble the conditioned compensatory response mechanism which both Wikler and Siegel have proposed.

Discussion

The authors found that the unconditioned response to hydromorphone in detoxified addicts was skin temperature increase, pupil constriction, and reports of feeling high and attenuation of withdrawal symptoms and craving. The CS presentations during training with hydromorphone elicited anticipatory responses which preceded these drug effects. These included autonomic changes such as skin temperature decrease and pupilary dilation. Subjectively, the subjects reported feeling high, increased craving for opiates, and a reduction in withdrawal symptoms.

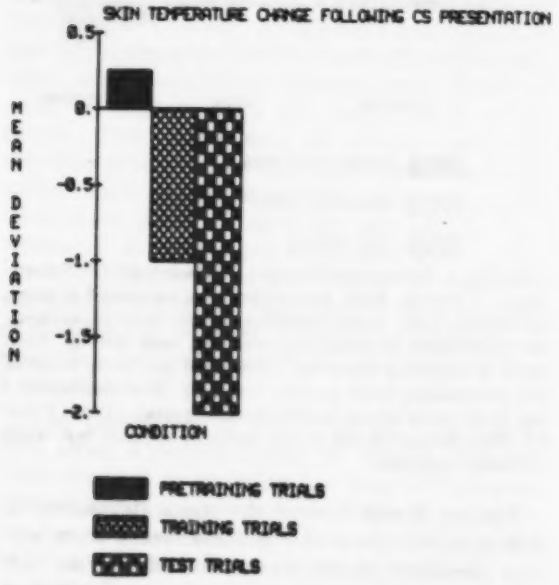

FIGURE 2. Skin Temperature Changes Following the CS Presentation. Mean deviations from session baseline periods during pretraining, training, and test trials. Each mean is based on two trials. The solid bar represents the pretraining trials. The crosshatched bar represents the training trials, and the checkered bar represents the test trials.

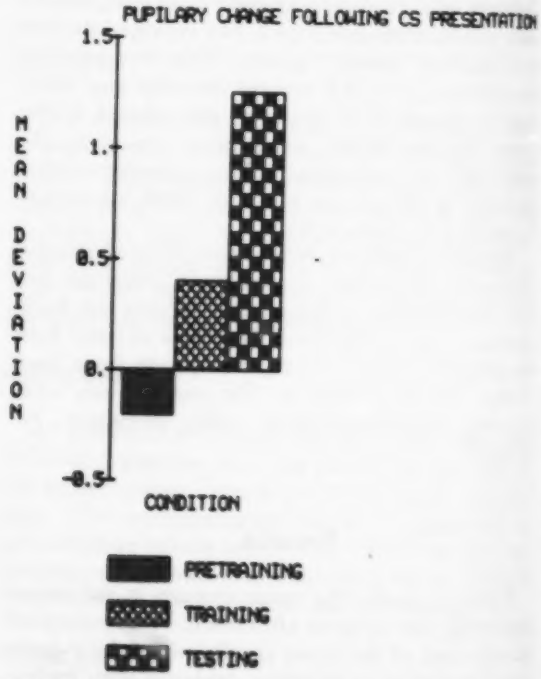

FIGURE 3. Pupillary Changes Following CS Presentation. Mean deviations from session baseline periods during pretraining, training, and test trials. Each mean is based on data from two trials. The solid bar represents pretraining trials, the crosshatched bar represents training trials, and the checkered bar represents test trials.

It was also found that during test trials, when physiological saline was infused instead of hydromorphone, CS presentation elicited skin temperature decrease, pupil dilation, and an increase in craving for opiates relative to baseline. No euphoria or high was reported. However, subjects experienced an increase in withdrawal symptoms. These results may appear contradictory, since subjects frequently reported feeling high prior to the drug infusion during training. Although they did not report feeling high on test trials, reports of withdrawal symptoms usually did not occur until 15 or 20 minutes after CS presentation. This suggests that the CS caused a brief delay in the onset of the withdrawal syndrome.

The authors believe these results indicate the complex nature of the CR to an opiate UCS in human addicts. It is comprised of both drug-negative and drug-positive components. Immediately following CS presentation, the subject may experience either euphoria or relief of withdrawal symptoms or delayed onset of withdrawal. However, in either case, eventually a negative affective reaction follows which is accompanied by an increased craving and withdrawal symptoms. Therefore the CR is essentially biphasic, a positive affective reaction followed in time by a negative reaction. Most addicts are relatively tolerant to opiates and therefore the negative component is in ascendency. This tends to reduce the initial positive drug effects when a good dose is administered. When a placebo or low dose is given, it results in labeling the negative affect as withdrawal symptoms.

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Lofexidine in Abrupt Methadone Withdrawal[1]

Arnold M. Washton, Ph.D.,[2] and Richard B. Resnick, M.D.[2]

Introduction

Previous studies have shown that the alpha-2 noradrenergic agonist, clonidine hydrochloride, is a safe and effective non-opiate treatment for opiate withdrawal and that clonidine can be extremely useful in facilitating a rapid transition from opiate dependence to aftercare treatment with the opiate antagonist, naltrexone (*see* review by Washton & Resnick 1981). However, clonidine is not without clinical risks and potential drawbacks. Clonidine's potent hypotensive and sedative effects have limited its clinical usefulness with some patients, suggesting that other alpha-2 noradrenergic agonists lacking these side effects might be safer and more efficacious.

Lofexidine hydrochloride (Merrell-Dow Pharmaceuticals) is an investigational analogue of clonidine that has been shown to significantly reduce opiate withdrawal in morphine-dependent rats (Shearman et al. 1980). Clinical testing of lofexidine as an antihypertensive agent has shown it to be less sedating and hypotensive than clonidine (Maner et al. 1980; St. John LaCorte et al. 1981). The present study was a preliminary clinical trial of lofexidine in abrupt methadone withdrawal. As in earlier studies with clonidine in this facility (Washton & Resnick 1981), the test of lofexidine's usefulness was conducted in an outpatient setting with the measure of success defined by induction onto naltrexone.

Method

The subjects were 15 methadone-dependent male outpatient volunteers who showed no evidence of medical or psychiatric illness and gave informed consent to the study which involved an abrupt switch from methadone to lofexidine. On Day 1, subjects received their usual methadone dose (10-25 mg) and began a self-administered lofexidine dose regimen of 0.1 mg two or three times daily. On Day 2, methadone was abruptly discontinued with subjects receiving a matched placebo methadone solution, and the lofexidine dosage was increased to 0.1 mg four times daily. Subsequently, the lofexidine dose was increased as needed to no more than 0.4 mg four times daily according to symptoms and side effects. All subjects were told that the detoxification procedure would take 11 days and that naltrexone could be started on Day 11 (10 days post-methadone), provided that they used no illicit opiates during the study as confirmed by the absence of a precipitated withdrawal reaction to intravenous naloxone challenge (2.0 mg) on Day 11. Subjects who did use illicit opiates during the first 10 days post-methadone were allowed to continue on lofexidine, and the naloxone challenge was postponed to the first opportunity where it posed minimal risk of precipitating a withdrawal reaction (i.e., to at least 5 days after the last opiate use) but no later than Day 21 of the study. The detoxification was considered successful if the subjects passed the naloxone challenge and started naltrexone on Days 11-21. Subjects who returned to using opiates and failed to begin naltrexone by Day 21 were considered unsuccessful.

Results

Successful detoxification and induction onto naltrexone was accomplished with 10 of the 15 subjects. All patients rated lofexidine as moderately to extremely effective in reducing most of the commonly experienced withdrawal symptoms. Insomnia, lethergy, and muscle/bone pain were the most frequent residual complaints. None of the 10 subjects reported unacceptable withdrawal symptoms while taking lofexidine. Those who failed to complete the detoxification procedure cited opiate craving rather than withdrawal discomfort as the major reason for returning to opiate use. No one reported oversedation, dizziness, or lightheadedness from lofexidine, despite rapid increases in the dose to as

[1]The authors' research studies cited in this paper were conducted in a treatment program at New York Medical College sponsored by the New York State Office of Alcoholism and Substance Abuse, Division of Substance Abuse Services. Research funds were provided by the National Institute on Drug Abuse, Boehringer Ingleheim Ltd., and Merrell-Dow Pharmaceuticals, Inc.

[2]Department of Psychiatry, Division of Drug Abuse Research and Treatment, New York Medical College, New York, NY 10029.

much as 1.6 mg per day within the first 5 days. The maximum daily lofexidine dose ranged from 0.6 mg to 1.6 mg across the 10 subjects with an average of 1.2 mg. There was no significant lowering of blood pressure (BP) even at the maximum lofexidine dose (mean prelofexidine BP, 115/74 mm Hg; mean BP at maximum dose 115/76 mm Hg). Dry mouth and mild drowsiness were the most commonly reported side effects. Upon study completion, reductions in the daily lofexidine dose by 0.2 to 0.6 mg per day produced no symptomatic complaints or significant changes in blood pressure.

Discussion

This open clinical trial provides preliminary evidence of lofexidine's efficacy in reducing symptoms of opiate withdrawal. The present findings are similar to earlier results with clonidine (Washton & Resnick 1981) in terms of detoxification success rates and withdrawal symptom relief, but lofexidine was found to be considerably less sedating and hypotensive. Lofexidine may therefore prove to be safer and more clinically useful than clonidine, especially in outpatient opiate detoxification. These findings suggest that lofexidine might allow opiate-addicted outpatients even greater access to naltrexone or drug-free modalities without hospital admission. A controlled study comparing lofexidine with gradual methadone detoxification is currently being conducted at this facility.

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Effects of Desipramine on Diurnal Rhythms of Plasma 3-Methoxy-4-Hydroxyphenylglycol (MHPG) in Depressed Patients[1]

Edward M. DeMet, Ph.D.,[2] Angelos E. Halaris, M.D., Ph.D.,[2] Harry E. Gwirtsman, M.D.,[2] Rochelle M. Reno, Ph.D.,[2] and Phyllis I. Becker, M.D.[2]

A number of studies have suggested that manic-depressive illness may be associated with a decrease in noradrenergic activity. A noradrenergic role is supported by findings of low levels of the major norepinephrine (NE) metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) in the urine and plasma of some depressed patients (Halaris & DeMet 1979; Maas et al. 1968). MHPG changes in these fluids are believed to largely reflect changes in central NE turnover (DeMet & Halaris 1979). However, it has been shown that successful treatment of depressed patients with tricyclic antidepressants fails to produce a sustained increase in urinary MHPG levels, as might be expected if NE activity were directly related to the depressed mood state (Beckmann & Goodwin 1975; Halaris & DeMet 1980). One possible explanation for this discrepancy could be related to the fact that MHPG levels follow a circadian rhythm with elevated levels during the daytime and reduced levels during the evening and night hours (Halaris & DeMet 1981; Wehr et al. 1980). Both of the above cited studies showed that the circadian rhythm of MHPG in manic-depressive patients was phase-advanced by 1 to 2 hours as compared to normal subjects. Moreover, another study has shown that the tricyclic antidepressant, imipramine, exerts effects on diurnal rhythms of adrenergic receptor binding in rat brain (Wirz-Justice et al. 1980). In that study, chronic

[1]This study was supported by USPHS Grant MH-35824 from the National Institute of Mental Health, and the Veterans Administration.

[2]Department of Psychiatry, UCLA School of Medicine and Veterans Administration Medical Center, Brentwood Division, Los Angeles, CA 90073.

Address reprint requests to: Edward M. DeMet, Ph.D., VA Hospital Brentwood, 11301 Wilshire Blvd., Los Angeles, CA 90073.

imipramine treatment resulted in a phase retardation of the normal diurnal rhythms of alpha- and beta-adrenergic receptor binding. Whether the antidepressant effect of these agents is directly related to their ability to delay the phase of the diurnal rhythm of NE remains to be established.

The present investigation was undertaken to determine whether treatment with a tricyclic antidepressant might cause a phase delay of the circadian pattern of NE turnover in depressed patients. Three hospitalized depressed patients meeting Research Diagnostic Criteria (RDC) for primary major depressive disorder, endogenous type, were compared with three normal volunteers. Patients were free of any psychoactive medication for at least 3 weeks prior to the study. No attempt was made to impose dietary or activity restrictions on either patients or volunteers, since no significant effect on MHPG blood levels had been found in preliminary studies. A history of alcohol use in either patients or volunteers served as exclusion criterion, and all subjects were requested to refrain from the use of any alcoholic beverages for at least three days prior to the experiment. A log of activity and foods ingested was maintained. A written informed consent was obtained from each participant in the study. Blood samples were obtained from an indwelling antecubital catheter which was kept patent by flushing it with sterile citrate-phosphate-dextrose buffer (CPD-A). A baseline diurnal rhythm of plasma MHPG was determined for each subject using the gas chromatographic method of Halaris et al. (1977). Blood samples were collected at 3-hour intervals around the clock, with the exception that the 6 a.m. sample was omitted in the patient collections. Patients were then treated with a daily dose of 150 mg desipramine-HCl (DMI) for a total of 4 weeks. Changes in mental status and clinical improvement were determined weekly by means of the Hamilton Rating Scale for Depression. The diurnal rhythm of MHPG levels in plasma was reexamined following the fourth week of treatment.

Figure 1 shows that both the normal volunteers and the depressed patients had pronounced diurnal rhythms of plasma MHPG levels. However, the rhythms differed in the two groups, with the depressed patients leading normal controls by about 3 hours. The averaged rhythms shown for both depressed patients and normals follow a true circadian rhythm with a 24-hour periodicity. Individual normal subjects also showed sinusoidal patterns with a 24-hour periodicity. When these rhythms for the normals were averaged, the resultant curve was actually slightly distorted as compared to the individual curves due to minor differences in intra-subject amplitude variability. The opposite was true of depressed patients. Individual patients significantly deviated from a 24-hour periodicity, and several exhibited secondary peaks in the late afternoon and evening. Averaging of the individual rhythms tended to mask these differences such that a secondary peak is only barely evident in Figure 1, and the net response approximates a 24-hour period. Both the amplitudes and baselines of the MHPG rhythms were similar in the depressed and normal subjects.

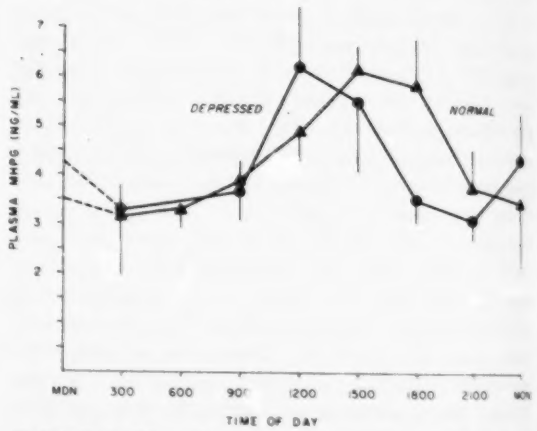

FIGURE 1. Diurnal pattern of plasma MHPG levels in three normal subjects (▲—▲) and three endogenously depressed patients (•—•).

All three patients showed significant improvement with DMI treatment, as evidenced by a decrease in Hamilton rating scores (change score = 23 ± 2.08 S.E.M.). Figure 2 shows that DMI treatment resulted in the normalization of the phase of diurnal plasma MHPG rhythms. This change was accompanied by a slight reduction in both the baseline MHPG level and the amplitude of the MHPG cycle. Normalization was evident in the individual rhythms as well as in the composite sample.

The results of the present study clearly showed that plasma MHPG rhythms were phase-advanced in the three endogenously depressed patients studied. Clinical improvement with DMI treat-

ment was associated with the normalization of the phase of the MHPG rhythm. The fact that phase normalization occurred in all three patients studied suggests that MHPG phase shifts may be specific biochemical indicators of clinical improvement. Since the amplitudes of the diurnal rhythms of normal and depressed subjects were actually more similar before DMI treatment than after, the results further suggest that behavioral normalization after tricyclic treatment may be independent of changes in the amplitude of noradrenergic activity. Finally, the present results suggest that the circadian pattern of MHPG is a state-dependent trait that may be of diagnostic value.

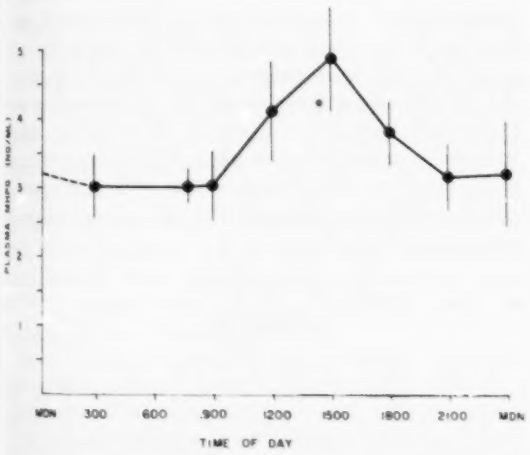

FIGURE 2. Diurnal pattern of plasma MHPG levels in the same three endogenously depressed patients after treatment with DMI.

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β-Endorphin, Cortisol, and Prolactin in Serum of Schizophrenic Patients During Long-Term Neuroleptic Treatment and After Withdrawal: Relationships to Psychopathology[1]

Dieter Naber, M.D.,[2] Margot Albus, M.D.,[2] Franz Muller, M.D.,[2] Horst Burke, M.D.,[2] Doris Welter,[2] Manfred Ackenheil, M.D.,[2] and Hanns Hippius, Prof., M.D.[2]

The effectiveness of neuroleptic maintenance therapy to prevent relapse of chronic schizophrenia is well established (Davis et al. 1976; Gardos & Cole 1976; Hogarty et al. 1976; Prien & Klett 1972; Wistedt 1981; Woggon 1979). However, there is evidence that some patients do not profit from neuroleptic treatment or even improve after withdrawal (Andrews et al. 1976; Leff & Wing 1971; Marder et al. 1979; Tobias & MacDonald 1974). With regard to the neuroleptics' serious side-effects such as tardive dyskinesia, there is a strong effort to minimize the neuroleptic dosage and to determine which patients do not require maintenance therapy.

Investigating any potential predictors for the effect of neuroleptic withdrawal in chronic schizophrenia, age of patients, duration of illness, and previous neuroleptic dosage have been found to correlate with psychopathological changes and probability of relapse (Davis et al. 1976; Marder et al. 1979; Prien & Klett 1972; Woggon 1979). In other studies, low serum level of prolactin was associated with early relapse after drug discontinuation (Brown & Laughren 1981; Zander et al. 1981). This study is an attempt to replicate these previous findings and to see whether serum levels of β-endorphin and cortisol are related to psychopathological changes after neuroleptic withdrawal.

Method

Twenty-four chronic schizophrenic patients, diagnosed according to the ICD-system, participated in the study. Leading symptoms were delusions, hallucinations, behavioral disorders, and disturbances of affect and energy level. Their age was 27 - 65 (mean ± SD 46 ± 8) years; they were treated with different neuroleptics for 1 - 24 (8 ± 7) years at a daily dosage of 560 ± 490 mg of chlorpromazine equivalents. After the first serum sampling, neuroleptic treatment was discontinued and placebo was given instead for 12 days. Blood was collected via an indwelling intravenous catheter from fasting, reclining patients in the morning 12 hours after the last neuroleptic dosage and again 12 days after drug withdrawal. The Brief Psychiatric Rating Scale (BPRS) was used to rate psychopathological syndromes on the 2 days of blood collection. Prolactin, cortisol, and β-endorphin were measured by commercially available radioimmunoassays (NEN). To increase the validity of these hormonal measurements, two individual samples 5 minutes apart were taken from each patient during neuroleptic treatment as well as after drug withdrawal. The statistical analyses were performed with the mean value of both samples.

Results

Serum levels of prolactin, β-endorphin, and cortisol during long-term neuroleptic treatment as well as after drug withdrawal are listed in Table 1. Drug withdrawal caused significant changes of all three hormones: Prolactin levels decreased (t-test, $df=23$; $t=3.92$, $p<0.001$), while levels of β-endorphin ($t=4.62$, $p<0.0005$), and cortisol ($t=5.19$, $p<0.0001$) both increased. Correlating serum levels during neuroleptic treatment and after withdrawal, significant relationships were found (Pearson correlation, $N=24$): prolactin $r=0.71$, $p<0.001$; β-endorphin $r=0.61$, $p<0.005$; cortisol $r=0.53$, $p<0.01$. The two serum samples, taken 5 minutes apart during neuroleptic treatment as well as after withdrawal, were also significantly correlated: prolactin $r=0.84$, $p<0.0001$ and $r=0.86$, $p<0.0001$; β-endorphin $r=0.67$, $p<0.001$ and $r=0.85$, $p<0.0001$; cortisol $r=0.67$, $p<0.001$ and $r=0.81$, $p<0.0001$. During withdrawal, β-endorphin and cortisol serum levels were significantly correlated ($r=0.63$, $p<0.001$).

[1]This work was supported by the Deutsche Forschungsgemeinschaft.
[2]Psychiatrische Klinik der Universität München, München, Federal Republic of Germany.

Table 1

Levels of Prolactin, β-Endorphin, and Cortisol in Serum of 24 Male Chronic Schizophrenic Patients During Long-Term Neuroleptic Therapy (NL) and After Drug Withdrawal for 12 Days (WL)

Hormone	NL Mean ± SD (% of Patient Above Normal Range)	WL Mean ± SD (% of Patient Above Normal Range)
Prolactin (ng/ml)	25.2 ± 22.6 (41%)	10.6 ± 12.2 (13%)
β-Endorphin (pg/0.1 ml)	8.9 ± 1.8 (4%)	11.4 ± 3.1 (46%)
Cortisol (μg/100 ml)	17.9 ± 4.5 (8%)	23.6 ± 5.4 (42%)

Normal range: Prolactin 5-20 ng/ml; β-endorphin 5-12 pg/0.1 ml; cortisol 12-25 μg/100ml.

Drug withdrawal caused distinct changes in the psychopathology of most patients, but within the whole group the total BPRS score did not change (43.6 ± 10.9 pts vs. 42.6 ± 12.2 pts). Of the five different subscales, only "anergia" showed a significant decrease (14.5 ± 5.2 pts vs. 12.5 ± 5.8 pts; $t=3.63$, $p<0.05$). Correlating hormonal measurements with psychopathological scores, only β-endorphin serum level after neuroleptic withdrawal was significantly related to total BPRS score ($r=-0.44$, $p<0.05$) and to "angergia" ($r=-0.46$, $p<0.05$).

Relationships between serum levels of prolactin, β-endorphin, and cortisol to changes of BPRS scores after drug withdrawal are listed in Table 2. Six subjects worsened (6-16 points) and 8 subjects improved (6-12 points) by more than 6 points of the total BPRS score. These two groups did not differ in serum levels of prolactin or cortisol, but improved subjects had significantly higher levels of β-endorphin during neuroleptic treatment ($10.0\pm2,1$ pg/0.1 ml vs. 7.5 ± 7.4 pg/0.1 ml; $t=3.15$, $p<0.02$) as well as after withdrawal (13.8 ± 1.7 pg/0.1 ml vs. 9.8 ± 3.5 pg/0.1 ml; $t=2.65$, $p<0.05$).

There were no significant relationships between BPRS scores or their changes after withdrawal and age, duration, or dosage of neuroleptic treatment.

Discussion

The individually very different psychopathological response to withdrawal of neuroleptics is in agreement with numerous previous studies (Andrews et al. 1976; Davis et al. 1976; Leff & Wing 1971; Prien & Klett 1972; Marder et al. 1979; Zander et al. 1981). However, looking for variables which discriminate between patients who improve and those who worsen after drug discontinuation, this study did not replicate findings that age, duration of illness, previous neuroleptic therapy (Davis et al. 1976; Marder et al. 1979; Prien & Klett 1972; Woggon 1979) or prolactin serum levels (Brown & Laughren 1981; Laughren et al. 1979; Zander et al. 1981) are valid predictors.

Only the β-endorphin serum level was found to correlate significantly with the effects on psychotic behavior: While patients with low levels mostly worsened, high levels of β-endorphin were associated with improvement or lack of change. It

Table 2

Relationships Between Hormonal Serum Levels in 24 Male Chronic Schizophrenic Patients During Neuroleptic Treatment (NL) and After 12 Days of Drug Withdrawal (WL) to Changes in BPRS Psychopathology Scores

	Changes of BPRS Psychopathology Scores (WL score-NL score, improvement = negative numbers)					
	Total Score	Anxiety Depress.	Anergia	Thought Disord.	Activat.	Hostility
Prolactin NL	−0.03	0.36	0.28	−0.25	−0.16	−0.16
Prolactin WL	−0.07	0.31	0.08	−0.15	−0.02	−0.12
β-Endorphin NL	−0.48*	−0.15	−0.54**	−0.23	0.17	−0.23
β-Endorphin WL	−0.41*	−0.23	−0.43*	0.17	−0.06	−0.45*
Cortisol NL	0.01	0.00	−0.17	0.03	0.10	0.13
Cortisol WL	−0.32	−0.32	−0.45*	0.08	0.12	0.01

Pearson correlation: * = $p<0.05$; ** $p<0.01$.

has to be considered that neuroleptic withdrawal for 12 days is a rather short period, but psychotic relapses often occur already within 8-14 days after discontinuation of long-term neuroleptic treatment (Davis et al. 1976; Zander et al. 1981). Further studies are obviously needed to investigate the possible relationship between the β-endorphin serum level and psychotic relapse following neuroleptic withdrawal.

The neuroendocrine results are similar to previous studies: Long-term neuroleptic treatment seems to induce tolerance of the tuberoinfundibular system, at least in some patients; therefore the prolactin-stimulating effect does not exist any more in all patients and the mean serum level is close to the normal range (Brown & Laughren 1981; Naber et al. 1979; Zander et al. 1981). The effect of neuroleptics on serum levels of β-endorphin in humans is controversial: Emrich et al. (1980) found a significant increase, but Brambilla et al. (1981) did not observe a significant change. Ongoing studies show that neuroleptic treatment for 2-6 weeks induces a significant increase of β-endorphin serum levels only in about 40 percent of patients (Naber et al. unpublished). The mostly normal levels found in this study could reflect the development of tolerance. The increase after neuroleptic withdrawal is probably a nonspecific stress effect, since coritsol, not affected by chronic neuroleptic therapy (Franzen 1971; Naber 1980), also increased significantly.

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Comments and suggestions are invited.

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Psychopharmacology Bulletin
National Institute of Mental Health
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